A METAPOPULATION MODEL FOR CHOLERA WITH VARIABLE MEDIA EFFICACY AND IMPERFECT VACCINE

BY

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Declaration

This thesis is my own work and has not been presented for a degree award in any other institution.

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This thesis has been submitted for examination with our approval as the university supervisors.

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Dedication

This work is dedicated to my children Boldon and Marlin, my parents Phanuel and Julia and my siblings Millicent, Peter, Benard, Dr. Jacinter, Lauryn and Verolin. Through your encouragements and prayers, this research has become possible.

Abstract

Cholera, a diarrheal disease caused by a pathogenic virulent bacteria known as *Vibrio cholerae*, affects both children and adults and can kill within hours if left untreated. It continues to persist in developing countries where there is inadequate access to clean water and sanitation facilities. Recent cholera metapopulation models assume a uniform efficacy of the control strategies across the communities involved and that, once vaccinated, the individuals are fully protected from the infection. These assumptions may not be entirely true or realistic since cholera vaccines do not confer 100% immunity and community specific demographics and the behavior of individuals are likely to affect the implementation and success of the control strategies. This study developed and analysed a metapopulation model for cholera with imperfect vaccine and variable media awareness as the control strategies. The results of stability analysis show that the disease free equilibrium point is both locally and globally asymptotically stable when the basic reproduction number is less than unity while the endemic equilibrium points are locally asymptotically stable when the basic reproduction number is greater than unity. Results from simulation analysis done using existing epidemiological data are in agreement with the analytic results. The simulation results further show that efficient media awareness reduces the transmission rate and that even with imperfect vaccine, cholera transmission is reduced. It is therefore advisable that health practitioners embrace the use of both vaccination and media awareness when designing and implementing community specific intervention strategies.

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Chapter 1

Introduction

1.1 Background of the Study

Cholera is a diarrheal infection caused by ingestion of food or water contaminated with a bacterium known as *Vibrio cholerae* (*V. cholerae*). There are more than 200 *O* serogroups of *Vibrio cholerae*, but only the serogroups 01 and 0139, have been known to cause cholera [1]. Serogroup 01 causes most of the outbreaks [2].

Cholera spread across the world from its original reservoir in the Ganges delta in India in the $19^{th}C$ killing millions of people across all continents. To date, seven cholera pandemics have occurred with the first six occurring from $1817-1923$, and were probably caused by *Vibrio cholerae* 01 of the classic biotype [3]. The seventh pandemic, the first to be recognized to have been caused by El Tor biotype of *Vibrio cholerae* strain [4], began in 1961 in Indonesia, affecting five continents by 1991 [3]. The spread just like in the previous outbreaks was facilitated by modern transportation and mass migrations [4] of especially the asymptomatically infected indi-

viduals. For example, the fourth pandemic began in the Ganges delta in 1863 and traveled with Muslim pilgrims to Mecca where it claimed about $30,000$ pilgrims. It later spread to Middle East, Russia, Europe, North America, Northern Africa and Zanzibar by travelers along inland water ways [5].

The disease is more common in developing countries especially in Africa, parts of Asia and South and Central America where there is inadequate access to safe drinking water and poor sanitation facilities. In the 21^{st}C, Sub-Saharan Africa bears the brunt of global cholera [2] where the countries face the dual challenges of improving both cholera treatment and access to basic health care, prevention and improved water and sanitation systems. For the last several years, Africa has reported over 95% of global cholera cases and 99% of global cholera deaths [6]. In Kenya, cholera is endemic in many parts of the country with sporadic outbreaks especially during rainy seasons and in informal settlements. Evidently, socio-economic differences between regions would determine the efficacy of some strategies especially those targeting sanitation and hygiene.

Humans and the aquatic environments are the main reservoirs for *Vibrio cholerae*. Majority of the infected individuals do not manifest any symptom, though the bacillus is present in their excrements [7]. The major signs and symptoms include profuse watery diarrhea and vomiting. Most of the cholera cases are presumptively diagnosed based on clinical suspicion in patients who present with severe acute watery diarrhea. Diagnosis is confirmed by laboratory isolation of *Vibrio cholerae* from stool cultures

performed on specific selected media. Rapid test like stool dipsticks can support the diagnosis in settings where stool culture is not readily available. However, due to the high morbidity of cholera, management should be initiated on the basis of clinical suspicion.

If left untreated, cholera can kill within hours [7]. Its treatment depends on the severity of the illness and level of dehydration. World Health Organization (WHO) recommends fluid management guided by the level of volume depletion and an assessment of the ongoing fluid loss. The lost fluids are replaced through oral and intravenous rehydration. Antibiotics are an adjunctive therapy for patients with severe volume depletion.

Public health goals that can help prevent cholera include improved hygiene and sanitation, provision of clean drinking water and public health education since it enhances awareness of the preventive measures. These can be achieved by drinking treated or boiled water, washing hands after visiting the toilet, before handling or eating food and proper preparation and storage of food.

WHO recommends oral cholera vaccines as part of the integrated control program in areas at risk of cholera outbreak [8]. Two internationally-licensed oral cholera vaccines are available. The Bivalent killed whole-cell vaccine (Shanchol) that contains killed whole cells of several biotypes and serotypes of *Vibrio cholerae* 01 and 0139 without supplemental cholera toxin B subunit. Its efficacy has been evaluated with trials done in In-

dia and Bangladesh, to be between 53% - 67% and persisted five years following vaccination [9]. WC-rBSC (Dukarol) is an oral cholera vaccine that contains killed whole cells of several biotypes and serotypes of *Vibrio cholerae* 01 in addition to recombinant cholera toxin B subunit. Its efficacy has been evaluated in several studies including studies done in Mozambique and Zanzibar to be about 78% [10], although it is not effective against *Vibrio cholerae* 0139.

A multifaceted approach is key to control of cholera, and to reduce related deaths. Actions targeting environmental conditions include the implementation of adapted long-term sustainable WASH (Water Sanitation and Hygiene) solutions to ensure use of safe water, basic sanitation and good hygiene practices to populations most at risk of cholera. Proper and timely management of cases in treatment centres, sufficient medical supplies, prompt awareness programs and public health education, personnel training to effectively manage cases, awareness, availability and accessibility of oral cholera vaccines are also vital aspects in the control of cholera.

The transmission dynamics of cholera is closely linked to inadequate access to clean and safe drinking water, poor hygiene and sanitation facilities with migration propagating its transmission as was witnessed during the fourth pandemic [4]. In Kenya, about 48% of the citizens lack access to basic sanitation solutions with 32% relying on unclean water sources like pods, shallow wells and rivers [11] which are always prone to contamination. The Kenyan informal settlements constitute about 54.7% of

the total population [12]. Vaccination against cholera has been shown in [13] to greatly alter its transmission dynamics and naturally lead to its elimination from the communities with time. Currently, the oral cholera vaccines approved by WHO only provides between 53% to 67% (Shanchol) and about 78% (Dukarol) protection against the infection with the latter being effective against *Vibrio cholerae* 001 only [9]. These clearly depicts that the vaccines do not confer total protection against cholera. Public awareness about the outbreak of cholera has been shown to greatly reduce the epidemic size and duration [1]. The impact of media awareness is likely to vary between communities due to factors like the education levels in different communities, the socio-economic status of each community, the availability of basic facilities and infrastructure among others. These factors may also affect the rate of vaccination in the communities.

1.2 Statement of the Problem

Poor sanitation and hygiene as well as lack of access to safe drinking water are challenges that continue to characterize much of Sub-Saharan Africa leading to the persistence of infections such as cholera, whose spread is facilitated by traveling or migration. Recent cholera metapopulation models with vaccination assume that once an individual is vaccinated, then they are fully protected and that the rate of vaccination in any two communities is uniform. These assumptions may not be entirely realistic since cholera vaccines only confer between 53% to 78% immunity and the literacy levels, socio-economic and infrastructural differences between communities is likely to affect the efficacy of media awareness and the

rates of vaccination.

1.3 Objectives of the Study

The main objective of this study was to develop and analyse a metapopulation model for cholera with imperfect vaccine and variable media awareness. The specific objectives of the study were:

(i) To formulate a mathematical model described by a set of ordinary differential equations for cholera transmission between two communities subject to an imperfect vaccine and variable media awareness.

(ii) To analyse the long term effects of imperfect vaccination and variable media awareness on the transmission dynamics of cholera between communities connected by migration.

(iii) To numerically simulate the effects of imperfect vaccine and variable media awareness as cholera control strategies.

1.4 Significance of the Study

Cholera, a highly infectious and fatal disease, is endemic in many parts of Sub-Saharan Africa majorly characterized by high poverty levels. Its spread is highly facilitated by migration or travel from one community to another. Similar control strategies applied across two communities with varying characteristics are likely to have varying outcomes. The results shall assist health practitioners in designing and implementing

community specific intervention strategies and re-emphasize the need for all individuals including the vaccinated to take precaution against the infection since cholera vaccines do not confer 100% immunity.

1.5 Justification of the Study

Cholera continues to persist in most developing countries where there is poor sanitation and hygiene facilities with movement of people playing a critical role in its transmission. Majority of the infected individuals do not manifest any symptom although the bacillus is present in their excrements potentially infecting both human and environmental sources. Cholera is extremely virulent and can kill within hours if left untreated, hence it is imperative to analyse the effects of control strategies on its transmission between communities.

Chapter 2

Literature Review

2.1 Introduction

Literature in mathematical modeling of cholera transmission dynamics, cholera models incorporating media awareness, cholera models with vaccination as one of the control strategies and epidemic models for disease transmission between communities linked by migration are the key areas of focus in this chapter.

2.2 Mathematical Models for Cholera Transmission

Cholera transmission dynamics depend mainly on the interactions between the human host, the pathogen, and the environment [15]. A number of mathematical models have been developed to study the disease transmission dynamics, to predict future outbreaks and to evaluate the control

strategies. A mathematical model [16] for cholera epidemiology was developed and analysed to examine the role of environmental reservoir in the persistence of endemic cholera and define the minimum conditions for the development of epidemic and endemic cholera. The endemic, epidemic and cholera free populations are the hypothetical communities used to illustrate the dynamics of cholera. The model results show that the reproduction number of cholera is a function of social and environmental factors, and that cholera outbreaks are triggered when the contact and contamination rates bring the reproduction number above the unit threshold. In order to minimize cholera outbreaks, emphasis is on the importance of drinking clean and treated water and improving the sanitary conditions of the communities to reduce contamination of aquatic reservoirs. This may be enhanced by sustained awareness campaigns.

In [15], a mathematical model was developed to unravel the interactions between the host, the bacterial pathogen and the bacteriophage in cholera outbreaks in endemic settings and in the emergent epidemic regions. The host immunity, the pathogen hyperinfectivity and the phages are the key factors that were considered, in order to control cholera outbreaks. The emphasis is on the importance of reducing human exposure to freshly passed stool, proper waste management at household level and enhancing house-based interventions like water chlorination and hand washing for disease prevention. It's noteworthy that the host immunity can be boosted by vaccination.

2.3 Mathematical Models for Cholera Transmission with Vaccination

Access to clean potable water, adequate sanitation, promotion of good WASH (Water, Sanitation and Hygiene) practices, promotion of handwashing and safe food handling practices are important aspects to be considered in the prevention and control of cholera. Vaccination can be complementary to these activities if implemented timely and effectively. A number of mathematical models have been developed and analysed to study the effects of vaccination in the transmission dynamics of cholera. A mathematical model for cholera epidemics which comprises seasonality, loss of host immunity and control mechanisms acting to reduce cholera transmission is formulated and analysed in [17]. The analysis indicates that control mechanisms such as vaccination, improved sanitary conditions and water treatment applied continuously can diminish the reproduction number to a value less than unity and prevent cholera transmission. Furthermore, mass vaccination in endemic areas or during epidemics can reduce or eradicate cholera outbreaks. This can also be enhanced by awareness programs through media coverage.

An SVR-B (Susceptible-Vaccinated-Recovered-Bacteria) cholera model with imperfect vaccination is presented in [18]. Global stability analysis based on the imperfect vaccine, the environment and multiple transmission pathways is performed. The results show that the reproduction number satisfies a threshold property with threshold value of one and that cholera can be eliminated from the community if the imperfect vac-

cine brings the reproduction number to a value less than unity. The analysis indicates that despite being imperfect, the vaccine will always reduce the reproduction number of the disease. This model only monitors the effect of imperfect vaccination as the only control strategy in cholera epidemics. The outbreak of cholera in Yemen, was modeled via an SITRV (Susceptible-Infected-Treated-Recovered-Vaccinated) mathematical model in [13]. Simulations with and without vaccination show that the introduction of vaccination from the beginning of the epidemic could have led to the natural elimination of the disease and the reduction in the number of mortalities. However, the movement of asymptomatically infected individuals, before the commencement of vaccination, is bound to pose a challenge in terms of disease control.

A mathematical model for the dynamics and optimal control strategies for cholera epidemics was developed and analysed in [19] under the interventions; vaccination, treatment and education awareness. The analysis indicates that vaccination and education campaigns should be applied from the start followed by treatment and that in the presence of vaccination, the susceptible individuals take longer to leave the susceptible class and the infected individuals take less time to recover. The impact of vaccination and education awareness may be greatly affected by migration between communities. The assessment of the effect, the control strategies have on cholera transmission dynamics is done in [20]. The analysis indicates that vaccinating the susceptible individuals increases the number of immuned-recovered in the population. The observation was that by quarantining the infected individuals, the disease contact rate between

the susceptible and infected is minimized hence the spread of cholera in the population is reduced. Also noted was that, proper surveillance, educational campaigns and sensitization, sanitation and vaccination are important aspects to consider in order to reduce or eradicate cholera. However, migration of infected individuals could affect the implementation and success of the control strategies.

2.4 Mathematical Models for Cholera Transmission with Media Awareness

Public awareness campaigns or media alerts about the outbreak of an infectious disease may greatly alter the dynamics of its transmission as susceptible individuals take precautions to prevent the infection. The role of media alert or awareness as a control strategy against cholera has been assessed through mathematical models. An SIRS epidemic model incorporating media coverage with time delay is formulated and analysed in [21]. The results show that, the time delay in media coverage cannot influence the stability of the disease-free equilibrium, but the stability of the endemic equilibrium. Emphasis was on the need to communicate about an outbreak of an epidemic as soon as it starts. However, a combination of control strategies would lead to a better outcome.

In [1], the impact of media coverage on the spread of cholera was investigated. Sensitivity analysis conducted indicates that reducing the rate of human-to-human and environment-to-human transmission, rate of the

recruitment of the susceptible individuals and the rate of human shedding of the *Vibrios* to the environment, will reduce the reproduction number and the disease spread. However, increasing the rate of media efficacy, pathogen concentration required for one to catch the disease, rate of recovery and death of *Vibrios*, reduces the reproduction number and the disease spread. The numerical analysis shows that in the presence of media coverage, the disease dies out faster. A cholera epidemic model [22] investigated the impact of awareness programs and time delays on cholera outbreaks. The analysis shows that media coverage lowers the outbreak size and decreases the severity of the outbreak. Media publicity should focus on how to guide people's behavioral changes and provide travel advisory where necessary as it is critical for the control of infectious diseases such as cholera.

2.5 Metapopulation Models for the Transmission of Infectious Diseases

A metapopulation model is a description of a system, involving spatially separated populations with regular movement of individuals, using mathematical concepts and language. A metapopulation model is developed and analysed in [23] to examine the spread of an infectious disease by the migration of exposed juvenile hosts. The analysis indicates that there is a continuous source of infection through migration of exposed individuals, and the migration of susceptible individuals can change the infection-free equilibrium population densities from their migration-free values. The

analysis shows that migration has an important effect in maintaining the infection in any population. Media awareness and alerts may affect the rate of migration of individuals across the communities. The impact of migration on the spread of cholera between two communities was investigated in [24]. The analysis indicates that, when communities are isolated, the disease would be more severe in a community with poorer facilities while the community with better facilities may only have a single outbreak with no recurrence of the disease. It's also noted that the disease may devastate the community with relatively better facilities due to the immigration of the infected individuals and unrestricted migration in cholera hit regions may result in introduction of the disease in unaffected areas. The socio-economic differences between communities connected via migration is likely to determine the efficacy of control measures against the spread of cholera.

The Telegraph News on 2^{nd} January 2019 reported that the severe outbreak of cholera in Yemen, in 2017, that was dubbed the worst in history was introduced by migration from East Africa. Scientists using genome sequencing found that migration was behind the introduction of the disease in Yemen and that the strain originated in South Asia in 2012, but spread to Yemen from East Africa as Yemen has long been a crossroads for trade and communications between Africa and Asia [25]. In [26], a metapopulation model is formulated to study the impact of vaccination on the spread of measles. Simulation results of different epidemiological classes show that most of the individuals undergoing treatment or vaccination join the recovered class and that vaccination has a positive impact

on measles incidence and prevalence in a metapopulation.

A metapopulation model for cholera dynamics between two communities, in the presence of controls was developed and analysed in [27]. Modeling optimal control for the dynamics of cholera between two communities linked by migration is performed. The effects of vaccination, water chlorination and proper hygiene is investigated. The analysis shows that, in the presence of controls, the infection may be eight times less devastating and that the duration of the infection in the community cannot be more than half the time it would, in the absence of controls. This model assumes uniform efficacy of the control strategies in the communities involved, and that vaccinated individuals are fully protected against the infection. These assumptions may not be entirely realistic since cholera vaccines are not 100% efficacious.

The mathematical models for cholera with vaccination have clearly shown that even with an imperfect vaccine, the transmission of cholera is greatly pared. However, none has actually analysed the effects of vaccination in the transmission of cholera between communities which are linked by migration. Media alerts about the outbreak of cholera has been analysed by mathematical models, and they have asserted that the spread of cholera is greatly reduced when media awareness is applied promptly. Its impact on the spread of cholera when communities are connected by migration has not been explored. Metapopulation models for cholera transmission dynamics analysed have shown that migration greatly affects the spread of cholera between communities. Their assumptions that cholera vaccines

confer total protection and that the rates of vaccination are uniform in the communities may not be entirely true. This model explored the impact of imperfect vaccine and variable media awareness in two communities connected by migration.

Chapter 3

Model Development, Analysis and Discussion

3.1 Introduction

Based on a system of ordinary differential equations, a mathematical model for cholera transmission dynamics in the two communities is formulated. Positivity and boundedness of the solutions is cheked by integration of the systems of equations at time $t \geq 0$. The basic and vaccine reproduction numbers for the model are calculated using the next generation matrix approach. The local stability of the disease free equilibrium is analysed by linearizing the model systems. The global stability of DFE is investigated using Castillo-Chavez theorem [29], existence of the Endemic Equilibria is checked using Descartes' Rule of Signs. The local stability of the Endemic Equilibria is analyzed by evaluating their Jacobian matrices, Sensitivity of the model parameters is calculated using the normalized forward sensitivity index and finally numerical simulations for the model have been performed using MATLAB.

3.2 Model Description and Formulation

A metapopulation model based on a system of ordinary differential equations for the dynamics of cholera between two communities connected via migration and in the presence of imperfect vaccine and variable media awareness is formulated in order to achieve the objectives of this study.

3.2.1 Model Assumptions

The following assumptions are critical in the development of the model.

(i) Each community is homogeneous in the sense that there are no socio-economic barriers to interaction and a special heterogeneity which is accounted for by the immigrations. This takes care of the complexity which would arise out of individual differences.

(ii) Migration of susceptible individuals from one community to another has a negligible impact on the disease transmission since they do not transmit the infection.

(iii) Vaccine protection isn't 100% efficacious [14] and therefore, the vaccinated individuals are susceptible to the infection but at a lower rate.

(iv) The symptomatically infected individuals are quarantined in hospitals for treatment as soon as they are identified.

(v) Recovered individuals develop some immunity after recovery, and cannot be infected again in one outbreak [14].

3.2.2 Model Variables and Parameters

In the model, the general population considered is divided into two main communities and each community is divided into four compartments based on their status with respect to cholera infection. Each community involves individuals who are susceptible (S_i), the susceptible individuals who have been vaccinated against cholera (V_i), those infected symptomatically and asymptomatically (I_i) and those individuals who have recovered (R_i) from the infection ($i = 1, 2$). The total population for each community is given by N_i, where;

$$N_i = S_i + V_i + I_i + R_i \tag{3.1}$$

This model accounts for movement of asymptomatically infected individuals from one community to another. This group plays a vital role in metapopulation transmission modeling of cholera since they contribute to the disease transmission for a relatively long time. The role played by the asymptomatically infected individuals range from person to person transmission as well as shedding of the pathogens into the aquatic reservoirs.

The recruitment of the susceptible individuals into the communities are at the rates Λ_1 and Λ_2 for the first and the second communities respectively. This intrinsic difference rate is mainly the difference of births, deaths and immigrations at the time of modeling. Vaccination of the susceptible individuals is at the rates ω_1 and ω_2 for the first and second communities respectively, with $0 < \sigma_i < 1$, for $i = 1, 2$ denoting the vaccine efficacy. This implies that when σ is close to one, the vaccine is very effective and

the disease transmission is low and when σ is close to zero, the vaccine is not effective and the disease transmission is high. Considering the relatively long vaccine protection period [7], this model excludes vaccinated individuals whose immunity has waned off to become susceptible.

The concentration of *Vibrios* in the environment is denoted by B_1 and B_2 for the first and second communities respectively. The susceptible individuals acquire cholera infection through ingestion of environmental *Vibrios* from contaminated water reservoirs at the rates λ_{ei} for $i = 1, 2$, where

$$\lambda_{ei} = (1 - \rho_i)\frac{\beta_{ei} B_i}{k + B_i} \tag{3.2}$$

The susceptible population is infected following ingestion of *Vibrios* from aquatic reservoirs at the rate β_{ei} and $(1 - \rho_i)\beta_{ei}$, is the reduced rate of ingestion of *Vibrios* from the environment due to media awareness, where $0 < \rho_i < 1$ measures the efficacy of media awareness. The half saturation constant of the pathogen population, enough to make an individual to contract the infection is denoted by $k > 0$. The saturation incidence function $\frac{\beta_{ei} B_i}{k+B_i}$ ensures boundedness of the incidence rate of infection from the environment and indicates that the incidence rate is gradual rather than linear. The susceptible individuals may also acquire cholera through human-to-human transmission after ingestion of hyperinfectious *Vibrios* at the rates λ_{hi} for $i = 1, 2$, where

$$\lambda_{hi} = (1 - \rho_i)\frac{\beta_{hi} I_i}{m + I_i} \tag{3.3}$$

β_{hi} is the effective contact rate for human-to-human transmission. The minimum contact rate with an infected person that can cause about 50%

chance of contracting the infection is denoted by m. $\frac{I_i}{m+I_i}$ is a continuous bounded function which takes into account the disease saturation. The natural death rates in the first and second communities are denoted by μ_1 and μ_2 respectively as it is assumed that $\mu_1 \neq \mu_2$ due to differences in socio-economic status of the two communities. The infected individuals recover from the infection at the rates γ_1 and γ_2 and suffer disease induced mortality at the rates δ_1 and δ_2 for the first and second communities respectively. The movement of asymptomatically infected individuals across the communities is at the rates a_{12} and a_{21} for the first and second communities respectively. Infected individuals shed bacteria into the environment at the rates ξ_1 and ξ_2 in the first and second communities respectively, with $(1-\rho_i)\xi_i$ for $i = 1, 2$, denoting the reduced shedding rate of pathogens by the infected individuals due to media awareness and the decay rates of the pathogens in the first and second communities is denoted by μ_{1p} and μ_{2p} respectively. The multiplication rates of pathogens in the aquatic reservoirs in the first and second communities is given by g_1 and g_2 respectively. The above description is captured in the flow chart diagram in Figure 3.1. A mathematical equivalent in terms of systems of equations is represented by equations (3.4) and (3.5).

Table 3.1: Model Variable Description

Variable	Symbol
Number of susceptible individuals in community i	S_i
Number of vaccinated individuals in community i	V_i
Number of infected individuals in community i	I_i
Number of recovered individuals in community i	R_i
Concentration of *Vibrios* in community i	B_i

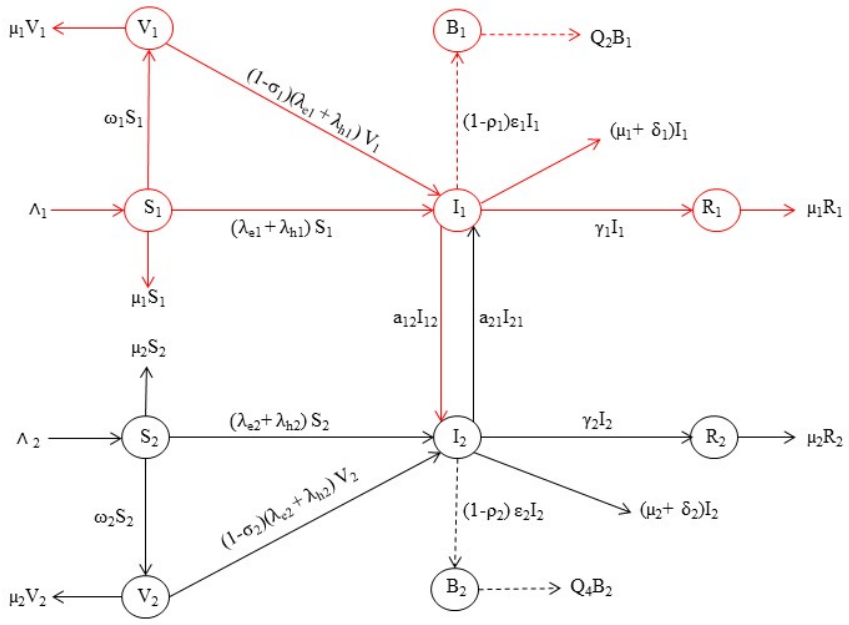

Figure 3.1: The Flow Diagram for the Metapopulation Model.

Table 3.2: Model Parameter Description

Parameter	Symbol
Recruitment rate into community i	Λ_i
Vaccination rate in community i	ω_i
Vaccine efficacy in community i	σ_i
Vibrios ingestion rate in community i	β_{ei}
Rate of contact with infectives in community i	β_{hi}
Efficacy of media awareness in community i	ρ_i
Half saturation constant of the pathogen	k
Minimum contact rate with the infected	m
Natural death rate in community i	μ_i
Rate of recovery in community i	γ_i
Disease induced mortality rate in community i	δ_i
Rate of shedding of *Vibrios* in community i	ξ_i
Decay rate of pathogen in community i	μ_{ip}
Multiplication rate of *Vibrios* in community i	g_i
Rate of migration of the infectives	a

3.2.3 The Model Equations

The system of equations for the first and second communities are respectively given by;

$$\begin{aligned}
\frac{dS_1}{dt} &= \Lambda_1 - \omega_1 S_1 - [\lambda_{e1} + \lambda_{h1}]S_1 - \mu_1 S_1, \qquad (3.4)\\
\frac{dV_1}{dt} &= \omega_1 S_1 - (1-\sigma_1)[\lambda_{e1} + \lambda_{h1}]V_1 - \mu_1 V_1,\\
\frac{dI_1}{dt} &= [\lambda_{e1} + \lambda_{h1}]S_1 + (1-\sigma_1)[\lambda_{e1} + \lambda_{h1}]V_1 + a_{21}I_2 - Q_1 I_1,\\
\frac{dR_1}{dt} &= \gamma_1 I_1 - \mu_1 R_1,\\
\frac{dB_1}{dt} &= (1-\rho_1)\xi_1 I_1 - Q_2 B_1,
\end{aligned}$$

and

$$\begin{aligned}
\frac{dS_2}{dt} &= \Lambda_2 - \omega_2 S_2 - [\lambda_{e2} + \lambda_{h2}]S_2 - \mu_2 S_2, \qquad (3.5)\\
\frac{dV_2}{dt} &= \omega_2 S_2 - (1-\sigma_2)[\lambda_{e2} + \lambda_{h2}]V_2 - \mu_2 V_2,\\
\frac{dI_2}{dt} &= [\lambda_{e2} + \lambda_{h2}]S_2 + (1-\sigma_2)[\lambda_{e2} + \lambda_{h2}]V_2 + a_{12}I_1 - Q_3 I_2,\\
\frac{dR_2}{dt} &= \gamma_2 I_2 - \mu_2 R_2,\\
\frac{dB_2}{dt} &= (1-\rho_2)\xi_2 I_2 - Q_4 B_2,
\end{aligned}$$

where $Q_1 = \mu_1 + \delta_1 + \gamma_1 + a_1$, $Q_2 = \mu_{1p} - g_1$, $Q_3 = \mu_2 + \delta_2 + \gamma_2 + a_2$, $Q_4 = \mu_{2p} - g_2$. Q_2 and Q_4 are positive such that in the presence of improved hygiene and sanitation and reduced shedding rate of the pathogens by the infected individuals, the bacteria cannot sustain themselves in the aquatic environment [16]. Since the first three and last equations in systems (3.4) and (3.5) are independent of the variable R, it

is therefore decoupled in both equations. Thus, it is enough to consider the following reduced systems of equations.

$$\begin{aligned}
\frac{dS_1}{dt} &= \Lambda_1 - \omega_1 S_1 - [\lambda_{e1} + \lambda_{h1}]S_1 - \mu_1 S_1, \qquad (3.6)\\
\frac{dV_1}{dt} &= \omega_1 S_1 - (1-\sigma_1)[\lambda_{e1} + \lambda_{h1}]V_1 - \mu_1 V_1,\\
\frac{dI_1}{dt} &= [\lambda_{e1} + \lambda_{h1}]S_1 + (1-\sigma_1)[\lambda_{e1} + \lambda_{h1}]V_1 + a_{21}I_2 - Q_1 I_1,\\
\frac{dB_1}{dt} &= (1-\rho_1)\xi_1 I_1 - Q_2 B_1,
\end{aligned}$$

and

$$\begin{aligned}
\frac{dS_2}{dt} &= \Lambda_2 - \omega_2 S_2 - [\lambda_{e2} + \lambda_{h2}]S_2 - \mu_2 S_2, \qquad (3.7)\\
\frac{dV_2}{dt} &= \omega_2 S_2 - (1-\sigma_2)[\lambda_{e2} + \lambda_{h2}]V_2 - \mu_2 V_2,\\
\frac{dI_2}{dt} &= [\lambda_{e2} + \lambda_{h2}]S_2 + (1-\sigma_2)[\lambda_{e2} + \lambda_{h2}]V_2 + a_{12}I_1 - Q_3 I_2,\\
\frac{dB_2}{dt} &= (1-\rho_2)\xi_2 I_2 - Q_4 B_2.
\end{aligned}$$

The initial conditions for the model are such that $S_i(0) = S_{0i} > 0$, $V_i(0) = V_{0i} \geq 0$, $I_i(0) = I_{0i} \geq 0$, and $B_i(0) = B_{0i} \geq 0$ for $i = 1, 2$. The model is well posed if all its solutions are positive and bounded in the invariat region Ω where $\Omega = \{(S_1, V_1, I_1, B_1, S_2, V_2, I_2, B_2) : N \leq \frac{\Lambda}{\mu}\}$.

3.3 Model Analysis

The well posedness of the model is established by showing that its solutions are positive and bounded.

3.3.1 Positivity of Solutions

Throughout this work, an assumption is made that the initial conditions of system (3.6) and system (3.7) are non-negative since the model monitors populations. Therefore, the initial conditions for the model are such that $S_i(0) = S_{0i} > 0$, $V_i(0) = V_{0i} \geq 0$, $I_i(0) = I_{0i} \geq 0$, and $B_i(0) = B_{0i} \geq 0$ for $i = 1, 2$. The total population in each community satisfies
$\frac{dN_i(t)}{dt} = \Lambda_i - \mu_i N_i - \delta_i I_i$

and the population size for the two communities is

$N(t) = \sum_{i=1}^{2}(N_i(t))$

Theorem 3.3.1
Let the initial conditions be $S_i(0) > 0$ *and* $\{V_i(0), I_i(0), B_i(0) \geq 0\}$, *then the solution set* $\{S_i(t), V_i(t), I_i(t), B_i(t)\}$ $(i = 1, 2)$ *of the model system* (3.6) *and* (3.7) *is non-negative for all* $t \geq 0$.

Proof. From the first equation of system (3.6) and system (3.7);

$$\begin{aligned} \frac{dS_i}{dt} &= \Lambda_i - \omega_i S_i - \lambda_{ei} S_i - \lambda_{hi} S_i - \mu_i S_i \\ \frac{dS_i}{dt} &\geq -[\omega_i + \lambda_{ei} + \lambda_{hi} + \mu_i] S_i \end{aligned}$$

Integrating by separation of variables yields;

$$\begin{aligned} \int \frac{dS_i}{S_i} &\geq -\int [\omega_i + \lambda_{ei} + \lambda_{hi} + \mu_i]dt \\ \ln S_i &\geq -[\omega_i + \lambda_{ei} + \lambda_{hi} + \mu_i]t + C \end{aligned}$$

for some constant C. Thus;

$$\begin{aligned} S_i(t) &\geq e^{-[\omega_i+\lambda_{ei}+\lambda_{hi}+\mu_i]t}.e^C \\ S_i(t) &\geq Ke^{-[\omega_i+\lambda_{ei}+\lambda_{hi}+\mu_i]t} \end{aligned}$$

where $K = e^C$. Hence, $S_i(t) \geq 0$ for all $t \geq 0$.
Similarly, it can also be shown that the other solutions, are also non-negative for all time $t \geq 0$. □

3.3.2 Boundedness of Solutions

The model solutions are shown to be bounded in the invariant region Ω where $\Omega = \{(S_1, V_1, I_1, B_1, S_2, V_2, I_2, B_2) : N \leq \frac{\Lambda}{\mu}\}$.

Theorem 3.3.2

The solutions of the model systems (3.6) *and* (3.7) *are contained in the feasible region* Ω.

PROOF. Assuming that the initial conditions for system (3.6) and system (3.7) are non-negative, $\Omega = \bigcup_{i=1}^{2} \Omega_i$ and that each community is a closed community with respect to the adjacent community, then the time derivative of $N_i(t)$ for $(i = 1, 2)$ is given by;

$$\frac{dN_i}{dt} = \Lambda_i - \mu_i(S_i + V_i + I_i + R_i) - \delta_i I_i, \tag{3.8}$$

therefore,

$$\frac{dN_i}{dt} + \mu_i N_i \leq \Lambda_i. \tag{3.9}$$

Solving inequality (3.9) using the integrating factor $e^{\mu_i t}$ gives;

$$N_i(t) \leq \frac{\Lambda_i}{\mu_i} + e^{-\mu_i t} C \tag{3.10}$$

for some positive constant C.

Using the initial condition $t = 0$, inequality (3.10) becomes;

$$N_i(0) \leq \frac{\Lambda_i}{\mu_i} + C \tag{3.11}$$

Taking the limit of inequality (3.10), as $t \to \infty$;

$$\lim_{t\to\infty} N_i(t) \leq \frac{\Lambda_i}{\mu_i}$$

which implies that for $i = 1, 2$,

$$0 < N_i(t) \leq \frac{\Lambda_i}{\mu_i} + C$$

for all $t \geq 0$. Hence the solutions of system (3.6) and system (3.7) are bounded in Ω. Therefore, the solutions are non-negative for all time $t \geq 0$ and bounded in the invariant region Ω, hence the model is mathematically

well posed and biologically meaningful in the feasible region Ω. □

3.4 Stability Analysis of the Equilibrium Points

An equilibrium point is defined as a steady state solution or a constant solution of a model. The equilibrium points of the model are determined by setting the right hand side of the system of equations to zero and solving each to get a constant solution. Epidemiological models usually have two equilibrium points that is Disease Free Equilibrium and Endemic Equilibrium. The Disease Free Equilibrium is a point where the disease is not present in the population while the Endemic Equilibrium is a point where the disease is persistent in the population. The existence of the equilibrium points with respect to the basic reproduction number is derived using the next generation matrix approach. The stability of the model is analysed in order determine the impact of imperfect vaccine and variable media awareness on the epidemiology of cholera between the two communities linked via migration.

The metapopulation model has four equilibrium points, that is the disease free equilibrium (E_0), the first and second boundary endemic equilibria (E_1) and (E_2) respectively and the interior endemic equilibrium (E_3) in

$\mathbb{R}$, where

$$\begin{aligned} E_0 &= (S_1, V_1, 0, 0, S_2, V_2, 0, 0) \in \mathbb{R}^8_+ \\ E_1 &= (S_1^*, V_1^*, I_1^*, B_1^*, S_2, V_2, 0, 0) \in \mathbb{R}^8_+ \\ E_2 &= (S_1, V_1, 0, 0, S_2^*, V_2^*, I_2^*, B_2^*) \in \mathbb{R}^8_+ \\ E_3 &= (S_1^*, V_1^*, I_1^*, B_1^*, S_2^*, V_2^*, I_2^*, B_2^*) \in \mathbb{R}^8_+ \end{aligned} \tag{3.12}$$

3.4.1 Basic Reproduction Number (R_0)

Basic reproduction number (R_0) is the average number of secondary infections caused by a single infected agent during his/her entire infectious period, in a completely susceptible population. It is a non-dimensional quantity in epidemiology as it sets the threshold in the study of a disease both for predicting its outbreak and for evaluating its control strategies. Thus, whether a disease becomes persistent or dies out in a community depends on the value of the reproduction number. Theoretically, if $R_0 < 1$, then every infectious individual will cause less than one secondary infection and hence the disease will die out and when $R_0 > 1$, then every infectious individual will cause more than one secondary infection, hence the disease will be persistent in the population. A larger value of R_0 may indicate the possibility of a major epidemic. The basic reproduction number for the model is determined using the next generation matrix approach by P. van den Driessche et al [28]. The basic and vaccine reproduction numbers for the two isolated communities are determined.

Considering the next generation matrix Z made up of two $m \times m$ matrices F and V such that

$Z = FV^{-1}$

and that

$F = \frac{\partial \mathcal{F}_i}{\partial x_j}(E_0)$ and $V = \frac{\partial \mathcal{V}_i}{\partial x_j}(E_0)$,

where F is the Jacobian evaluated at E_0 of $\mathcal{F}_i$ which is the rate of appearance of new infections in compartment i, V is the Jacobian evaluated at E_0 of $\mathcal{V}_i$ which is the rate of transfer of individuals from compartment i by all other means. $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$ where $\mathcal{V}_i^-$ is the rate of transfer of individuals out of compartment i and $\mathcal{V}_i^+$ is the rate of transfer of individuals into compartment i by all other means. The basic reproduction number is given as the spectral radius of matrix Z. Thus,

$R_0 = \rho(FV^{-1})$.

The third and fourth equations of system (3.6) are used to compute the vaccine reproduction number (R_{V1}) for the first community. Thus, computing $\mathcal{F}_1$ and $\mathcal{V}_1$, gives;

$$\mathcal{F}_1 = \begin{pmatrix} \frac{\alpha_1\beta_{e1}B_1}{k+B_1}S_1 + \frac{\alpha_1\beta_{h1}I_1}{m+I_1}S_1 + \eta_1\left[\frac{\alpha_1\beta_{e1}B_1}{k+B_1}V_1 + \frac{\alpha_1\beta_{h1}I_1}{m+I_1}V_1\right] \\ 0 \end{pmatrix}$$

and

$$\mathcal{V}_1 = \begin{pmatrix} Q_1 I_1 \\ -\alpha_1\xi_1 I_1 + Q_2 B_1 \end{pmatrix}$$

where $\alpha_1 = 1 - \rho_1$ and $\eta_1 = 1 - \sigma_1$.

Now, calculating the Jacobian matrices of $\mathcal{F}_1$ and $\mathcal{V}_1$ at E_0 yields,

$$F_1 = \begin{pmatrix} \frac{\alpha_1\beta_{h1}\Lambda_1}{m(\mu_1+\omega_1)} + \eta_1\frac{\alpha_1\beta_{h1}\Lambda_1\omega_1}{\mu_1(\mu_1+\omega_1)m} & \frac{\alpha_1\beta_{e1}\Lambda_1}{k(\mu_1+\omega_1)} + \eta_1\frac{\alpha_1\beta_{e1}\Lambda_1\omega_1}{\mu_1(\mu_1+\omega_1)k} \\ 0 & 0 \end{pmatrix}$$

and

$$V_1 = \begin{pmatrix} Q_1 & 0 \\ -\alpha_1\xi_1 & Q_2 \end{pmatrix}.$$

The inverse of matrix V_1 is given by

$$V_1^{-1} = \begin{pmatrix} \frac{1}{Q_1} & 0 \\ \frac{\alpha_1\xi_1}{Q_1Q_2} & \frac{1}{Q_2} \end{pmatrix}.$$

Therefore

$$F_1V_1^{-1} = \begin{pmatrix} \frac{(\mu_1+\eta_1\omega_1)(\alpha_1\beta_{h1}\Lambda_1kQ_2+\alpha_1^2\beta_{e1}\Lambda_1\xi_1m)}{\mu_1(\mu_1+\omega_1)kQ_1Q_2m} & \frac{\alpha_1\beta_{e1}\Lambda_1\mu_1+\eta_1\alpha_1\beta_{e1}\Lambda_1\omega_1}{\mu_1(\mu_1+\omega_1)kQ_2} \\ 0 & 0 \end{pmatrix} \tag{3.13}$$

The vaccine reproduction number (R_{V1}) for the first community, is obtained by taking the dominant eigenvalue of equation (3.13). Thus

$$R_{V1} = \frac{(\mu_1+\eta_1\omega_1)(\alpha_1\beta_{h1}\Lambda_1kQ_2+\alpha_1^2\beta_{e1}\Lambda_1\xi_1m)}{\mu_1(\mu_1+\omega_1)kQ_1Q_2m} \tag{3.14}$$

Using the third and fourth equations of system (3.7), the vaccine reproduction number (R_{V2}) for the second community is thus computed as;

$$R_{V2} = \frac{(\mu_2+\eta_2\omega_2)(\alpha_2\beta_{h2}\Lambda_2kQ_4+\alpha_2^2\beta_{e2}\Lambda_2\xi_2m)}{\mu_2(\mu_2+\omega_2)kQ_3Q_4m} \tag{3.15}$$

In the absence of intervention strategies, the parameters ω_i and ρ_i for $i = 1, 2$ are set to zero and the basic reproduction number (R_{01}) for the first community, is given by;

$$R_{01} = \frac{\beta_{h1}\Lambda_1kQ_2+\beta_{e1}\Lambda_1\xi_1m}{\mu_1kQ_1Q_2m} \tag{3.16}$$

and the basic reproduction number (R_{02}) for the second community is given by;

$$R_{02} = \frac{\beta_{h2}\Lambda_2 kQ_4 + \beta_{e2}\Lambda_2\xi_2 m}{\mu_2 kQ_3Q_4 m} \tag{3.17}$$

3.4.2 Disease Free Equilibrium (E_0)

The Disease Free Equilibrium for systems (3.6) and (3.7) is obtained by setting $\frac{dS_i}{dt} = \frac{dV_i}{dt} = \frac{dI_i}{dt} = \frac{dB_i}{dt} = 0$ for $i = 1, 2$ and in the absence of the disease, $I_i = B_i = 0$, so that the system of equations in (3.6) and (3.7) reduces to

$$\begin{aligned} \frac{dS_{0i}}{dt} &= \Lambda_i - \omega_i S_i - \mu_i S_i \\ \frac{dV_{0i}}{dt} &= \omega_i S_i - \mu_i V_i \end{aligned}$$

Hence, the Disease Free Equilibrium of the model is given by;

$$E_0 = \left(\frac{\Lambda_1}{\mu_1 + \omega_1}, \frac{\Lambda_1\omega_1}{\mu_1(\mu_1 + \omega_1)}, 0, 0, \frac{\Lambda_2}{\mu_2 + \omega_2}, \frac{\Lambda_2\omega_2}{\mu_2(\mu_2 + \omega_2)}, 0, 0\right) \tag{3.18}$$

3.4.3 Local Stability of the Disease Free Equilibrium

To investigate the local stability of the disease free equilibrium $E_0 = (S_1, V_1, 0, 0, S_2, V_2, 0, 0)$, the method described in [28] is employed to linearize system (3.6) and system (3.7).

Theorem 3.4.1

The disease free equilibrium (E_0) is locally asymptotically stable if $R_V < 1$ and unstable otherwise.

PROOF. The Jacobian matrix of system (3.6) evaluated at E_0 is given by;

$$J(E_{01}) = \begin{pmatrix} -(\omega_1+\mu_1) & 0 & -\frac{\alpha_1\beta_{h1}\Lambda_1}{(\mu_1+\omega_1)m} & -\frac{\alpha_1\beta_{e1}\Lambda_1}{(\mu_1+\omega_1)k} \\ \omega_1 & -\mu_1 & -\frac{\eta_1\alpha_1\beta_{h1}\Lambda_1\omega_1}{\mu_1(\mu_1+\omega_1)m} & -\frac{\eta_1\alpha_1\beta_{e1}\Lambda_1\omega_1}{\mu_1(\mu_1+\omega_1)k} \\ 0 & 0 & \frac{\alpha_1\beta_{h1}\Lambda_1}{m(\mu_1+\omega_1)} + \frac{\eta_1\alpha_1\beta_{h1}\Lambda_1\omega_1}{\mu_1(\mu_1+\omega_1)m} - Q_1 & \frac{\alpha_1\beta_{e1}\Lambda_1}{k(\mu_1+\omega_1)} + \frac{\eta_1\alpha_1\beta_{e1}\Lambda_1\omega_1}{\mu_1(\mu_1+\omega_1)k} \\ 0 & 0 & \alpha_1\xi_1 & -Q_2 \end{pmatrix} \tag{3.19}$$

An equilibrium point is locally asymptotically stable if its Jacobian matrix has a negative trace and a positive determinant or if all its eigenvalues have negative real parts [26]. The Jacobian matrix $J(E_{01})$ has two distinct negative eigenvalues given by $-\mu_1$ and $-(\omega_1+\mu_1)$. The local stability of the disease free equilibrium is studied by examining the trace and determinant of the reduced matrix B defined by;

$$B = \begin{pmatrix} \frac{\alpha_1\beta_{h1}\Lambda_1}{m(\mu_1+\omega_1)} + \frac{\eta_1\alpha_1\beta_{h1}\Lambda_1\omega_1}{\mu_1(\mu_1+\omega_1)m} - Q_1 & \frac{\alpha_1\beta_{e1}\Lambda_1}{k(\mu_1+\omega_1)} + \frac{\eta_1\alpha_1\beta_{e1}\Lambda_1\omega_1}{\mu_1(\mu_1+\omega_1)k} \\ \alpha_1\xi_1 & -Q_2 \end{pmatrix} \tag{3.20}$$

Let Tr denote the Trace and Det denote the Determinant of the matrix B as outlined in [1]. For the eigenvalues of B to be negative, then $Det(B) > 0$ and $Tr(B) < 0$. The conditions that will make this to hold are thus determined.

For $Det(B) > 0$, then

$$\frac{\alpha_1\beta_{h1}\Lambda_1Q_2}{(\mu_1+\omega_1)m} + \frac{\eta_1\alpha_1\beta_{h1}\Lambda_1\omega_1Q_2}{\mu_1(\mu_1+\omega_1)m} + \frac{\alpha_1^2\beta_{e1}\Lambda_1\xi_1}{k(\mu_1+\omega_1)} + \frac{\eta_1\alpha_1^2\beta_{e1}\Lambda_1\omega_1\xi_1}{\mu_1(\mu_1+\omega_1)k} < Q_1Q_2. \tag{3.21}$$

Simplifying inequality (3.21) yields;

$$\frac{(\mu_1+\eta_1\omega_1)(\alpha_1\beta_{h1}\Lambda_1 kQ_2+\alpha_1^2\beta_{e1}\Lambda_1\xi_1 m)}{\mu_1(\mu_1+\omega_1)kQ_1Q_2m}<1. \tag{3.22}$$

Since the LHS of inequality (3.22) is equal to R_{V1}, it implies that the determinant of B can only be positive if $R_{V1}<1$.

For $Tr(B)<0$, then,

$$\frac{\alpha_1\beta_{h1}\Lambda_1(\mu_1+\eta_1\omega_1)}{\mu_1(\mu_1+\omega_1)m}-Q_1<0. \tag{3.23}$$

Making Q_1 the subject of equation (3.14), yields;

$$Q_1=\frac{(\mu_1+\eta_1\omega_1)(\alpha_1\beta_{h1}\Lambda_1 kQ_2+\alpha_1^2\beta_{e1}\Lambda_1\xi_1 m)}{\mu_1(\mu_1+\omega_1)kQ_2mR_{V1}}. \tag{3.24}$$

Substituting equation (3.24) into inequality (3.23) gives;

$$\frac{\alpha_1\beta_{h1}\Lambda_1(\mu_1+\eta_1\omega_1)}{\mu_1(\mu_1+\omega_1)m}-\frac{(\mu_1+\eta_1\omega_1)(\alpha_1\beta_{h1}\Lambda_1 kQ_2+\alpha_1^2\beta_{e1}\Lambda_1\xi_1 m)}{\mu_1(\mu_1+\omega_1)kQ_2mR_{V1}}<0. \tag{3.25}$$

Simplifying inequality (3.25) yields;

$$\frac{\phi_1\alpha_1\Lambda_1}{\mu_1(\mu_1+\omega_1)m}\left[\beta_{h1}\left(1-\frac{1}{R_{V1}}\right)-\frac{\alpha_1\beta_{e1}\xi_1 m}{kQ_2R_{V1}}\right]<0. \tag{3.26}$$

Since $\frac{\alpha_1\beta_{e1}\xi_1 m}{kQ_2R_{V1}}<0$, it is therefore enough to consider;

$$\frac{\phi_1\alpha_1\Lambda_1}{\mu_1(\mu_1+\omega_1)m}\left[\beta_{h1}\left(1-\frac{1}{R_{V1}}\right)\right]<0. \tag{3.27}$$

which can only hold if $R_{V1}<1$ implying that the $Tr(B)<0$ if $R_{V1}<$

1. Hence, the disease free equilibrium is locally asymptotically stable if $R_{V1} < 1$. □

REMARK 3.4.2

Similarly, it can also be shown that the disease free equilibrium of the second community is also locally asymptotically stable when $R_{V2} < 1$.

3.4.4 Global Stability of the Disease Free Equilibrium

Castillo-Chavez approach [29] is used to investigate the global stability of the disease free equilibrium by rewriting system (3.6) and system (3.7) in the form;

$$\begin{aligned} \frac{dX}{dt} &= F(X, Z) \\ \frac{dZ}{dt} &= G(X, Z), G(X, 0) = 0, \end{aligned} \tag{3.28}$$

where $X = (S_1, V_1, S_2, V_2)$, $X \in \mathbb{R}^4$ denotes (its components) the uninfected individuals while $Z = (I_1, B_1, I_2, B_2)$, $Z \in \mathbb{R}^4$ denotes (its components) the infected individuals. $U_0 = (X^*, 0)$ is the disease free equilibrium of system (3.28).

These two conditions must be met for local asymptotic stability [29].

(H1) For $\frac{dX}{dt} = F(X, 0)$, X^* is globally asymptotically stable (g.a.s)

(H2) $G(X, Z) = AZ - \widehat{G}(X, Z)$, $\widehat{G}(X, Z) \geq 0$ for $(X, Z) \in \Omega$

where $A = D_Z G(X^*, 0)$ is a Metzler Matrix (the off diagonal elements are non-negative) and Ω is the region where the model makes biological

sense. If system (3.6) and system (3.7) satisfy condition (H1) and (H2) above, then the following theorem will hold.

Theorem 3.4.3

The fixed point $U_0 = (X^*, 0)$ *is a global asymptotic stable equilibrium of* (3.28) *provided* $R_V < 1$ *(l.a.s) and that the assumptions (H1) and (H2) are satisfied.*

PROOF. Since $X = (S_1, V_1, S_2, V_2)$ and $Z = (I_1, B_1, I_2, B_2)$,

$$F(X,0) = \begin{pmatrix} \Lambda_1 - \omega_1 S_1 - \mu_1 S_1 \\ \omega_1 S_1 - \mu_1 V_1 \\ \Lambda_2 - \omega_2 S_2 - \mu_2 S_2 \\ \omega_2 S_2 - \mu_2 V_2 \end{pmatrix}.$$

$$G(X,Z) = AZ - \widehat{G}(X,Z).$$

The matrix A is given by

$$A = \begin{pmatrix} \frac{\alpha_1 \beta_{h1} d_1}{m} - Q_1 & \frac{\alpha_1 \beta_{e1} d_1}{k} & a_{21} & 0 \\ \alpha_1 \xi_1 & -Q_2 & 0 & 0 \\ a_{12} & 0 & \frac{\alpha_2 \beta_{h2} d_2}{m} - Q_3 & \frac{\alpha_2 \beta_{e2} d_2}{k} \\ 0 & 0 & \alpha_2 \xi_2 & -Q_4 \end{pmatrix}$$

where $d_1 = S_1 + \eta_1 V_1$ and $d_2 = S_2 + \eta_2 V_2$.

$$AZ = \begin{pmatrix} \frac{\alpha_1 \beta_{h1} d_1 I_1}{m} - Q_1 I_1 + \frac{\alpha_1 \beta_{e1} d_1 B_1}{k} + a_{21} I_2 \\ \alpha_1 \xi_1 I_1 - Q_2 B_1 \\ a_{12} I_1 + \frac{\alpha_2 \beta_{h2} d_2 I_2}{m} - Q_3 I_2 + \frac{\alpha_2 \beta_{e2} d_2 B_2}{k} \\ \alpha_2 \xi_2 I_2 - Q_4 B_2 \end{pmatrix}$$

$G(X,Z)$ is given by

$$G(X,Z)=\begin{pmatrix} (\frac{\alpha_1\beta_{e1}B_1}{k+B_1}+\frac{\alpha_1\beta_{h1}I_1}{m+I_1})S_1+\eta_1(\frac{\alpha_1\beta_{e1}B_1}{k+B_1}+\frac{\alpha_1\beta_{h1}I_1}{m+I_1})V_1+a_{21}I_2-Q_1I_1 \\ \alpha_1\xi_1I_1-Q_2B_1 \\ (\frac{\alpha_2\beta_{e2}B_2}{k+B_2}+\frac{\alpha_2\beta_{h2}I_2}{m+I_2})S_2+\eta_2(\frac{\alpha_2\beta_{e2}B_2}{k+B_2}+\frac{\alpha_2\beta_{h2}I_2}{m+I_2})V_2+a_{12}I_1-Q_3I_2 \\ \alpha_2\xi_2I_2-Q_4B_2 \end{pmatrix}$$

and

$$\widehat{G}(X,Z)=\begin{pmatrix} \frac{\alpha_1\beta_{h1}I_1^2S_1}{m(m+I_1)}+\frac{\eta_1\alpha_1\beta_{h1}I_1^2V_1}{m(m+I_1)}+\frac{\alpha_1\beta_{e1}B_1^2S_1}{k(k+B_1)}+\frac{\eta_1\alpha_1\beta_{e1}B_1^2V_1}{k(k+B_1)} \\ 0 \\ \frac{\alpha_2\beta_{h2}I_2^2S_2}{m(m+I_2)}+\frac{\eta_2\alpha_2\beta_{h2}I_2^2V_2}{m(m+I_2)}+\frac{\alpha_2\beta_{e2}B_2^2S_2}{k(k+B_2)}+\frac{\eta_2\alpha_2\beta_{e2}B_2^2V_2}{k(k+B_2)} \\ 0 \end{pmatrix}$$

Since all the parameters used are positive and $0<\alpha_i,\eta_i<1$ for $i=1,2$, $\widehat{G}(X,Z)\geq 0$. Hence, conditions (H1) and (H2) have been met. Thus, E_0 is globally asymptotically stable (g.a.s). □

3.4.5 Boundary Endemic Steady State

The model has boundary endemic equilibrium point when the infection is persistent in one community but is absent in the other. The boundary endemic equilibrium points are obtained by setting the equations of system (3.6) and system (3.7) to zero. Note that at the first boundary endemic equilibrium point ($E_1=[S_1^*,V_1^*,I_1^*,B_1^*,S_2,V_2,0,0]$), $I_2=B_2=0$ and the disease is persistent only in the first community and at the second boundary endemic equilibrium point ($E_2=[S_1,V_1,0,0,S_2^*,V_2^*,I_2^*,B_2^*]$), $I_1=B_1=0$ and the disease is persistent only in the second community.

Theorem 3.4.4

The first boundary endemic equilibrium point $E_1(S_1^*, V_1^*, I_1^*, B_1^*, S_2, V_2, 0, 0)$ *exists provided that* $R_{V1} > 1$ *and* $R_{V2} < 1$.

PROOF. For the existence of the first boundary endemic equilibrium, the equations of system (3.6) and system (3.7) at E_1 become;

$$\begin{aligned} 0 &= \Lambda_1 - \omega_1 S_1 - \lambda_{e1}^* S_1 - \lambda_{h1}^* S_1 - \mu_1 S_1 \\ 0 &= \omega_1 S_1 - \eta_1[\lambda_{e1}^* V_1 + \lambda_{h1}^* V_1] - \mu_1 V_1 \\ 0 &= \lambda_{e1}^* S_1 + \lambda_{h1}^* S_1 + \eta_1[\lambda_{e1}^* V_1 + \lambda_{h1}^* V_1] - Q_1 I_1^* \\ 0 &= \alpha_1 \xi_1 I_1^* - Q_2 B_1^* \\ 0 &= \Lambda_2 - \omega_2 S_2 - \mu_2 S_2 \\ 0 &= \omega_2 S_2 - \mu_2 V_2, \end{aligned} \tag{3.29}$$

where;

$$\lambda_{ei}^* = (1-\rho_i)\frac{\beta_{ei} B_i^*}{k + B_i^*}, \qquad and \qquad \lambda_{hi}^* = (1-\rho_i)\frac{\beta_{hi} I_i^*}{m + I_i^*}$$

and I_i^* and B_i^* are the infected individuals and concentration of *Vibrios* in aquatic reserviors respectively, in a community where cholera infection is persistent.

Therefore, the fourth equation of system (3.29) yields;

$$B_1^* = \frac{\alpha_1 \xi_1 I_1^*}{Q_2}. \tag{3.30}$$

Substituting equation (3.30) and the limiting values of S_1 and V_1 into the

third equation of equation (3.29) and simplifying yields

$$AI_1^{*3} + BI_1^{*2} + CI_1^* = 0 \tag{3.31}$$

where

$A = -\alpha_1\xi_1\mu_1\tau_1Q_1$

$B = \phi_1(\alpha_1^2\beta_{e1}\Lambda_1\xi_1 + \alpha_1^2\beta_{h1}\Lambda_1\xi_1) - \mu_1\tau_1Q_1(kQ_2 + \alpha_1\xi_1 m)$

$C = \phi_1(\alpha_1^2\beta_{e1}\Lambda_1\xi_1 m + \alpha_1\beta_{h1}\Lambda_1 kQ_2) - kQ_2 m\mu_1Q_1\tau_1$

$\tau_1 = \mu_1 + \omega_1, \qquad \phi_1 = \mu_1 + \eta_1\omega_1$

From equation (3.31), $I_1^* = 0$ is one of the solutions of system (3.6) and system (3.7). This corresponds to the disease free equilibrium (E_0) and the other solutions when $I_1^* \neq 0$ gives the relationship between the susceptible, the vaccinated and the infected individuals in the first community. The equation;

$$AI_1^{*2} + BI_1^* + C = 0. \tag{3.32}$$

is thus considered. The first boundary endemic equilibrium of the system exists if the roots of equation (3.32) are real and positive. Descartes' rule of signs is used to check the possible number of real roots of the polynomial. The number of positive real roots of a polynomial is either equal to the number of sign changes in the coefficients or less than this by an even number. Analysis of the coefficients of equation (3.32) is done by first checking the sign of A. Since all the parameters used are positive, $\alpha_1 = 1 - \rho_1$, $(0 < \rho_1 < 1)$, the sign of A is negative. Next, the sign of C

is checked by considering

$$C = \phi_1(\alpha_1^2\beta_{e1}\Lambda_1\xi_1 m + \alpha_1\beta_{h1}\Lambda_1 kQ_2) - kQ_2 m\mu_1 Q_1\tau_1$$

which may be expressed as;

$$C = \left[\frac{\phi_1(\alpha_1^2\beta_{e1}\Lambda_1\xi_1 m + \alpha_1\beta_{h1}\Lambda_1 kQ_2)}{kQ_2 m\mu_1 Q_1\tau_1} - 1\right] kQ_2 m\mu_1 Q_1\tau_1. \tag{3.33}$$

Substituting equation (3.14) into equation (3.33) yields;

$$C = [R_{V1} - 1]kQ_2 m\mu_1 Q_1\tau_1. \tag{3.34}$$

Thus $C > 0$ iff $R_{V1} > 1$. Since A is negative and C is positive, it implies that there is at least one sign change regardless of the sign of B. Therefore, equation (3.32) has at least one positive real root. Hence, the first boundary endemic equilibrium point (E_1) exists. □

Remark 3.4.5

In a similar manner, it can be shown that the second boundary endemic equilirium point (E_2) also exists when $R_{V2} > 1$.

3.4.6 Local Stability of the First Boundary Endemic Steady State (E_1)

Cholera is endemic or persistent in the first community if $S_1^*, V_1^*, I_1^*, B_1^* > 0$ for all $t > 0$. The local stability of the first boundary endemic steady state analysis is given in the following theorem;

Theorem 3.4.6

The first boundary endemic equilibrium of system (3.6) and system (3.7) is locally asymptotically stable when $R_{V1} > 1$ *and* $R_{V2} < 1$.

PROOF. For the local stability of the first boundary endemic equilibrium point, the eigenvalues of the Jacobian matrix evaluated at the first boundary endemic equilibrium point (E_1), must have negative real parts. The Jacobian matrix evaluated at E_1 is given by;

$$J(E_1) = \begin{pmatrix} -f_0 & 0 & -f_1 & -f_2 & 0 & 0 \\ \omega_1 & -f_3 & -f_4 & -f_5 & 0 & 0 \\ f_6 & f_7 & f_8 - Q_1 & f_9 & 0 & 0 \\ 0 & 0 & \alpha_1\xi_1 & -Q_2 & 0 & 0 \\ 0 & 0 & 0 & 0 & -(\mu_2+\omega_2) & 0 \\ 0 & 0 & 0 & 0 & \omega_2 & -\mu_2 \end{pmatrix} \tag{3.35}$$

where

$f_0 = \omega_1 + \mu_1 + \frac{\alpha_1\beta_{e1}B_1}{k+B_1} + \frac{\alpha_1\beta_{h1}I_1}{m+I_1}$ $\quad$ $f_1 = \frac{\alpha_1\beta_{h1}\Lambda_1 m}{(\mu_1+\omega_1)(m+I_1)^2}$

$f_2 = \frac{\alpha_1\beta_{e1}\Lambda_1 k}{(\mu_1+\omega_1)(k+B_1)^2}$ $\quad$ $f_3 = \mu_1 + \frac{\eta_1\alpha_1\beta_{e1}B_1}{k+B_1} + \frac{\eta_1\alpha_1\beta_{h1}I_1}{m+I_1}$

$f_4 = \frac{\eta_1\alpha_1\beta_{h1}\Lambda_1\omega_1 m}{\mu_1(\mu_1+\omega_1)(m+I_1)^2}$ $\quad$ $f_5 = \frac{\eta_1\alpha_1\beta_{e1}\Lambda_1\omega_1 k}{\mu_1(\mu_1+\omega_1)(k+B_1)^2}$

$f_6 = \frac{\alpha_1\beta_{e1}B_1}{k+B_1} + \frac{\alpha_1\beta_{h1}I_1}{m+I_1}$ $\quad$ $f_7 = \frac{\eta_1\alpha_1\beta_{e1}B_1}{k+B_1} + \frac{\eta_1\alpha_1\beta_{h1}I_1}{m+I_1}$

$f_8 = \frac{\alpha_1\beta_{h1}\Lambda_1 m\phi_1}{\mu_1(\mu_1+\omega_1)(m+I_1^*)^2}$ $\quad$ $f_9 = \frac{\alpha_1\beta_{e1}\Lambda_1\phi_1 k}{\mu_1(\mu_1+\omega_1)(k+B_1)^2}$.

Clearly, the Jacobian matrix $J(E_1)$ has two distinct negative eigenvalues given by $-\mu_2$ and $-(\mu_2+\omega_2)$. The other eigenvalues can be computed by

determining the solution of the system given by;

$$\begin{vmatrix} \lambda + f_0 & 0 & -f_1 & -f_2 \\ \omega_1 & \lambda + f_3 & -f_4 & -f_5 \\ f_6 & f_7 & \lambda - f_8 + Q_1 & f_9 \\ 0 & 0 & \alpha_1\xi_1 & \lambda + Q_2 \end{vmatrix} = 0 \tag{3.36}$$

From equation (3.36), the characteristic equation of $J(E_1)$ is given by;

$$\lambda^4 + a_0\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0 \tag{3.37}$$

where

$a_0 = f_0 + f_3 + Q_1 + Q_2 - f_8$

$a_1 = f_0f_3 + f_1f_6 + f_4f_7 + f_0Q_1 + f_3Q_1 + f_0Q_2 + f_3Q_2 + Q_1Q_2 - f_8Q_2 - f_0f_8 - f_3f_8 - \alpha_1\xi_1f_9$

$a_2 = f_1f_3f_6 + f_0f_4f_7 - f_0f_3f_8 + f_0f_3Q_1 + f_0f_3Q_2 + f_1f_6Q_2 + f_4f_7Q_2 - f_0f_8Q_2 - f_3f_8Q_2 + f_0Q_1Q_2 + f_3Q_1Q_2 + \alpha_1\xi_1f_2f_6 + \alpha_1\xi_1f_5f_7 - \alpha_1\xi_1f_0f_9 - \alpha_1\xi_1f_3f_9 + \omega_1f_1f_7$

$a_3 = f_1f_3f_6Q_2 + f_0f_4f_7Q_2 - f_0f_3f_8Q_2 + f_0f_3Q_1Q_2 + \alpha_1\xi_1f_2f_3f_6 + \alpha_1\xi_1f_0f_5f_7 - \alpha_1\xi_1f_0f_3f_9 + \omega_1f_1f_7Q_2 + \alpha_1\xi_1\omega_1f_2f_7.$

The number of possible negative zeros of equation (3.37) depends on the signs of a_0, a_1, a_2 and a_3. This can be analysed using Descartes' Rule of Signs of the polynomial given by;

$$P(\lambda) = a_0\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0 \tag{3.38}$$

From this Rule, the number of negative real zeros of $P(\lambda)$ is either equal to the variations in sign of $P(-\lambda)$ or less than this by an even number.

The possibilities of negative roots of equation (3.38) is as summarized in Table 3.3. From the table, the maximum number of variations in signs of $P(-\lambda)$ is three, hence, the polynomial (3.38) has three negative roots. Thus, $J(E_1)$ has five negative real zeros. Therefore, the first boundary steady state is locally asymptotically stable if $R_{V1} > 1$ and $R_{V2} < 1$. □

REMARK 3.4.7

Similarly, the second boundary endemic steady state can also be shown to be locally asymptotically stable if $R_{V1} < 1$ and $R_{V2} > 1$.

Table 3.3: The Zeros of Characteristic Equation (3.38)

Cases	a_0	a_1	a_2	a_3	$R_{V1} > 1$	Sign Change	No. of $-$ Roots
1	$+$	$-$	$-$	$+$	$R_{V1} > 1$	2	$2, 0$
2	$+$	$-$	$+$	$+$	$R_{V1} > 1$	2	$2, 0$
3	$-$	$-$	$+$	$-$	$R_{V1} > 1$	2	$2, 0$
4	$+$	$+$	$-$	$-$	$R_{V1} > 1$	1	0
5	$-$	$-$	$+$	$+$	$R_{V1} > 1$	1	0
6	$+$	$+$	$+$	$-$	$R_{V1} > 1$	1	0
7	$-$	$+$	$-$	$+$	$R_{V1} > 1$	3	$3, 1$
8	$-$	$-$	$-$	$-$	$R_{V1} > 1$	0	0

3.4.7 Interior Endemic Equilibrium Point (E_3)

The model system has a non-trivial equilibrium point in the presence of infection in both communities, known as Interior Endemic equilibrium

point given by $E_3 = [S_1^*, V_1^*, I_1^*, B_1^*, S_2^*, V_2^*, I_2^*, B_2^*] \in \mathbb{R}_+^8$. This is the point when $I_i^* > 0$ and $B_i^* > 0$ for $i = 1, 2$, in the two communities.

Theorem 3.4.8

The interior endemic equilibrium point exists provided $R_{V1} > 1$ *and* $R_{V2} > 1$.

PROOF. At the interior endemic equilibrium point;

$$\begin{aligned}
0 &< \left(\frac{\alpha_1\beta_{e1}B_1^*}{k+B_1^*} + \frac{\alpha_1\beta_{h1}I_1^*}{m+I_1^*}\right)S_1 + \eta_1\left(\frac{\alpha_1\beta_{e1}B_1^*}{k+B_1^*} + \frac{\alpha_1\beta_{h1}I_1^*}{m+I_1^*}\right)V_1 - Q_1I_1^* \\
0 &< \alpha_1\xi_1I_1^* - Q_2B_1^* \qquad (3.39) \\
0 &< \left(\frac{\alpha_2\beta_{e2}B_2^*}{k+B_2^*} + \frac{\alpha_2\beta_{h2}I_2^*}{m+I_2^*}\right)S_2 + \eta_2\left(\frac{\alpha_2\beta_{e2}B_2^*}{k+B_2^*} + \frac{\alpha_2\beta_{h2}I_2^*}{m+I_2^*}\right)V_2 - Q_3I_2^* \\
0 &< \alpha_2\xi_2I_2^* - Q_4B_2^*
\end{aligned}$$

From the second and fourth equations of inequality (3.39);

$$\begin{aligned}
B_1^* &< \frac{\alpha_1\xi_1I_1^*}{Q_2} \\
B_2^* &< \frac{\alpha_2\xi_2I_2^*}{Q_4}. \qquad (3.40)
\end{aligned}$$

Substituting equation (3.30) and the limiting values of S_1 and V_1 into the first equation of inequality (3.39) and solving for I_1^* yields equation (3.31) which had been shown in *Theorem 3.4.3* to have at least one positive real root. Hence, $I_1^* > 0$ when $R_{V1} > 1$. It is also clear that $I_2^* > 0$ when $R_{V2} > 1$. These imply that $B_1^* > 0$ and $B_2^* > 0$. Therefore the interior endemic equilibrium point (E_3) exists when $R_{V1} > 1$ and $R_{V2} > 1$. □

3.4.8 Local Stability of the Interior Endemic Steady State

The local stability of the interior endemic equilibrium point is given by the following theorem.

Theorem 3.4.9

The interior endemic equilibrium of systems (3.6) and (3.7) is locally asymptotically stable when $R_{V1} > 1$ *and* $R_{V2} > 1$.

Proof. To investigate the local stability of the interior endemic equilibrium point (E_3), the model systems (3.6) and (3.7), are linearized at E_3. The Jacobian matrix at E_3 is given by;

$$J(E_3) = \begin{pmatrix} -f_0 & 0 & -f_1 & -f_2 & 0 & 0 & 0 & 0 \\ \omega_1 & -f_3 & -f_4 & -f_5 & 0 & 0 & 0 & 0 \\ f_6 & f_7 & f_8 - Q_1 & f_9 & 0 & 0 & a_{21} & 0 \\ 0 & 0 & \alpha_1\xi_1 & -Q_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -g_0 & 0 & -g_1 & -g_2 \\ 0 & 0 & 0 & 0 & \omega_2 & -g_3 & -g_4 & -g_5 \\ 0 & 0 & a_{12} & 0 & g_6 & g_7 & g_8 - Q_3 & f_9 \\ 0 & 0 & 0 & 0 & 0 & 0 & \alpha_2\xi_2 & -Q_4 \end{pmatrix} \tag{3.41}$$

where

$g_0 = \omega_2 + \mu_2 + \frac{\alpha_2\beta_{e2}B_2}{k+B_2} + \frac{\alpha_2\beta_{h2}I_2}{m+I_2}$, $\quad g_1 = \frac{\alpha_2\beta_{h2}\Lambda_2 m}{(\mu_2+\omega_2)(m+I_2)^2}$,

$g_2 = \frac{\alpha_2\beta_{e2}\Lambda_2 k}{(\mu_2+\omega_2)(k+B_2)^2}$, $\quad g_3 = \mu_2 + \frac{\eta_2\alpha_2\beta_{e2}B_2}{k+B_2} + \frac{\eta_2\alpha_2\beta_{h2}I_2}{m+I_2}$,

$g_4 = \frac{\eta_2\alpha_2\beta_{h2}\Lambda_2\omega_2 m}{\mu_2(\mu_2+\omega_2)(m+I_2)^2}$, $\quad g_5 = \frac{\eta_2\alpha_2\beta_{e2}\Lambda_2\omega_2 k}{\mu_2(\mu_2+\omega_2)(k+B_2)^2}$,

$g_6 = \frac{\alpha_2\beta_{e2}B_2}{k+B_2} + \frac{\alpha_2\beta_{h1}I_2}{m+I_2}$, $\quad g_7 = \frac{\eta_2\alpha_2\beta_{e2}B_2}{k+B_2} + \frac{\eta_2\alpha_2\beta_{h2}I_2}{m+I_2}$,

$g_8 = \frac{\alpha_2\beta_{h2}\Lambda_2 m\phi_2}{\mu_2(\mu_2+\omega_2)(m+I_2^*)^2}$, $g_9 = \frac{\alpha_2\beta_{e2}\Lambda_2\phi_2 k}{\mu_2(\mu_2+\omega_2)(k+B_2)^2}$.

The Jacobian matrix $J(E_3)$ can be re-written in the form

$$J(E_3) = \begin{pmatrix} J_{11} & J_{12} \\ J_{21} & J_{22} \end{pmatrix} \tag{3.42}$$

where

$$J_{11} = \begin{pmatrix} -f_0 & 0 & -f_1 & -f_2 \\ \omega_1 & -f_3 & -f_4 & -f_5 \\ f_6 & f_7 & f_8 - Q_1 & f_9 \\ 0 & 0 & \alpha_1\xi_1 & -Q_2 \end{pmatrix} \tag{3.43}$$

and

$$J_{22} = \begin{pmatrix} -g_0 & 0 & -g_1 & -g_2 \\ \omega_2 & -g_3 & -g_4 & -g_5 \\ g_6 & g_7 & g_8 - Q_3 & g_9 \\ 0 & 0 & \alpha_2\xi_2 & -Q_4 \end{pmatrix} \tag{3.44}$$

It's clear from *Theorem 3.4.4* that J_{11} and J_{22} have negative real roots hence, $J(E_3)$ has negative real zeros and the interior endemic equilibrium point (E_3) is locally asymptotically stable. □

3.5 Sensitivity Analysis

Sensitivity analysis on the vaccine reproduction number with respect to the model parameters is carried out to assess the relative impact of each of the parameters in the transmission and prevalence of cholera. It enables us to determine the robustness of the model predictions to parameter

values and to discover the parameters that have a high impact on R_V and should be targeted by intervention strategies. The normalized forward sensitivity index is used to calculate the sensitivity of the parameters. The normalized forward sensitivity index of the vaccine reproduction number, R_V, with respect to a parameter, U, is defined as:

$$P_U^{R_V} = \frac{\partial R_V}{\partial U} \times \frac{U}{R_V}.$$

The sensitivity of R_{Vi} on β_{hi} is now given by;

$$P_{\beta_{hi}}^{R_{Vi}} = \frac{\partial R_{Vi}}{\partial \beta_{hi}} \times \frac{\beta_{hi}}{R_{Vi}},$$

where

$$\frac{\partial R_{Vi}}{\partial \beta_{hi}} = \frac{(\mu_i + \eta_i\omega_i)\alpha_i\Lambda_i kQ_2}{\mu_i(\mu_i + \omega_i)kQ_1Q_2m}$$

and

$$\frac{\beta_{hi}}{R_{Vi}} = \frac{(\mu_i + \omega_i)\beta_{hi}\mu_i kQ_1Q_2m}{(\mu_i + \eta_i\omega_i)(\alpha_i\beta_{hi}\Lambda_i kQ_2 + \alpha_i^2\beta_{ei}\Lambda_i\xi_i m)}.$$

Therefore

$$P_{\beta_{hi}}^{R_{Vi}} = \frac{\beta_{hi}kQ_2}{\beta_{hi}kQ_2 + \alpha_i\beta_{ei}\xi_i m}$$

The sensitivity indices for the other parameters are as shown in Table 3.4.

Table 3.4: Sensitivity Indices for the Model Parameters.

Parameter	Sensitivity Index
Λ_i	1
k	-1
μ_i	$\frac{\beta_{hi}kQ_2[(\mu_i^2+\mu_i\omega_i)(\mu_i+\delta_i+\gamma_i)-(\mu_i(3\mu_i+2\delta_i+2\gamma_i)+\omega_i(2\mu_i+\delta_i+\gamma_i))]}{(\beta_{hi}kQ_2m+\beta_{ei}\xi_im\eta_i\omega_i)(\mu_i^2+\mu_i\omega_i)(\mu_i+\delta_i+\gamma_i)}$
ρ_i	$-\frac{\rho_i(\beta_{hi}kQ_2+(1-\rho_i)2\beta_{e1}\xi_im)}{\beta_{hi}kQ_2+2\beta_{e1}\xi_im}$
ω_i	$\frac{(1+\omega_i\sigma_i-\sigma_i-\omega_i-\mu_i)\omega_i}{\mu_i+\omega_i-\sigma_i\omega_i}$
m	$\frac{2\alpha_i\beta_{ei}\xi_im-\beta_{hi}kQ_2}{\beta_{hi}kQ_2+\alpha_i\beta_{ei}\xi_i}$
ξ_i	$\frac{\xi_i(\beta_{hi}kQ_2+\alpha_i\beta_{ei}m)}{\beta_{hi}kQ_2+\alpha_i\beta_{ei}\xi_im}$
β_{ei}	$\frac{\alpha_i\beta_{ei}\xi_im}{\beta_{hi}kQ_2+\alpha_i\beta_{ei}\xi_im}$
σ_i	$-\frac{\omega_i\sigma_i}{\mu_i+(1-\sigma_i)\omega_i}$
γ_i	$-\frac{\gamma_i}{\mu_i+\gamma_i+\delta_i}$
δ_i	$-\frac{\delta_i}{\mu_i+\gamma_i+\delta_i}$
μ_{ip}	$-\frac{\mu_{ip}}{\mu_{ip}-g_i}$
g_i	$\frac{g_i}{\mu_{ip}-g_i}$

From the sensitivity analysis, the parameters β_{hi}, β_{ei}, Λ_i, ξ_i, and g_i have positive sensitivity indices implying that lowering their levels leads to a reduction in the R_{Vi} hence reducing the disease spread. The parameters k, m, ω_i, σ_i, ρ_i, γ_i, and μ_{ip}, have negative sensitivity indices. This means that an increase in their levels results in a decrease of R_{Vi}. Thus the intervention strategies that lower the rate of ingestion of *Vibrios* from aquatic reservoirs, the contact rate between the infected and susceptible individ-

uals and the shedding rate of pathogen by the both symptomatically and asymptomatically infected individuals like vaccination, media awareness and education campaigns should be emphasized and administered by the health practitioners in order to lower the transmission rate of cholera in any given population.

3.6 Numerical Simulations

Numerical Simulations to validate the analytical findings and illustrate the long term dynamics of the systems have been performed using MATLAB.

3.6.1 Parameter Values

The parameter values used have been selected from some published literatures as shown in Table 3.3.

3.6.2 Simulations and Interpretations

The following initial values of the variables, $S_i(t) = 10000$, $V_i(t) = 100$, $I_i(t) = 5$, $R_i(t) = 0$ and $B_i(t) = 100$, are considered in order to illustrate the behavior of the solutions with time. When the parameter values in Table 3.3 are used to find R_V, $R_{V1} = 0.422452 < 1$ and $R_{V2} = 0.240175 < 1$.

Table 3.5: Model Parameter Values

Parameter	Value	Source
Λ_i	$9.6274 * 10^{-5}$ $(/day)$	[1]
ω_i	0.78 $(/day)$	$Varies$
σ_i	0.68 $(/day)$	$Estimate$
β_{e1}	0.075 $(/day)$	[30]
β_{e2}	0.01694 $(/day)$	[13]
β_{h1}	0.0005 $(/day)$	[31]
β_{h2}	0.00125 $(/day)$	$Estimate$
ρ_i	0.75	$Varies$
k	10^6 $cells/l$	$Estimate$
m	0.00001	[1]
μ_1	0.02 $(/day)$	[24],[32]
μ_2	$5.48 * 10^{-5}$ $(/day)$	[33]
γ_1	0.015 $(/day)$	[34]
γ_2	0.2 $(/day)$	[13]
δ_1	0.013 $(/day)$	[18]
δ_2	$4.0 * 10^{-4}$ $(/day)$	[1]
ξ_i	50 $(/day)$	[27]
μ_{ip}	1.06 $(/day)$	[27],[33]
g_i	0.73 $(/day)$	[27],[33]

The simulation results are presented in the figures below.

Figures 3.2 indicates that when $R_V < 1$, all the trajectories of the infected population converge to zero regardless of the presence of interven-

tion strategies. This pinpoints that the cholera free state can only be asymptotically stable in line with *Theorem 3.4.1.* It also shows that the epidemic size is greatly reduced when vaccination and media awareness are simultaneously deployed.

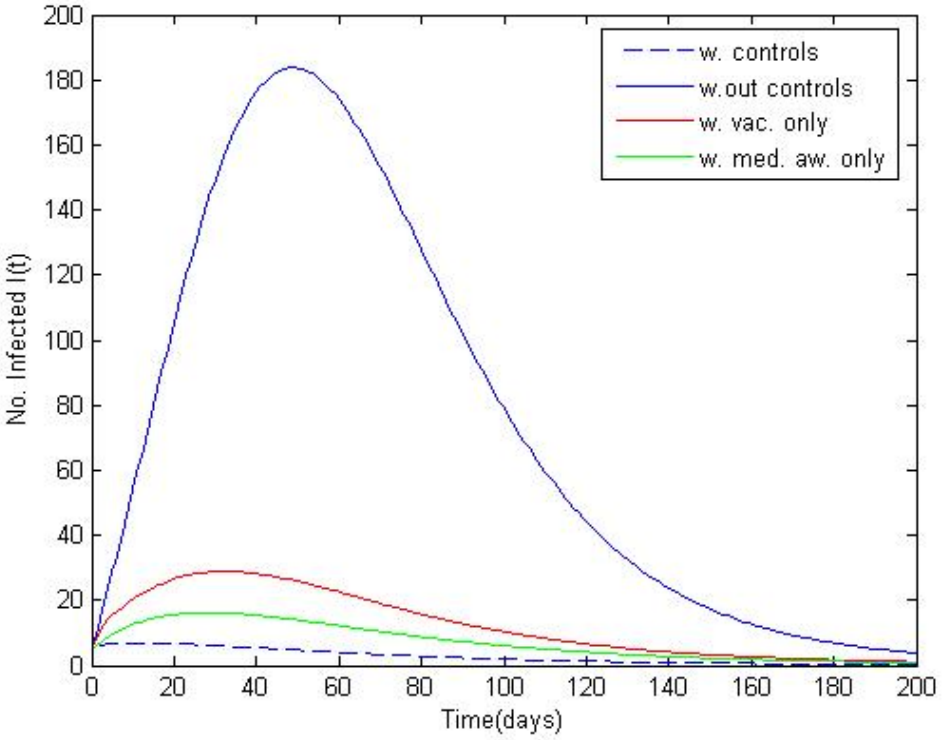

Figure 3.2: The Number of Infectives when $R_{V1} < 1$.

Figure 3.3 evinces that both vaccination and media awareness lower the spread of cholera with time, and that each has an inverse relationship with the spread of the disease. This is clearly seen when the rates of vaccination (ω_i) and the efficacy of the impact of media coverage (ρ_i) are varied. Therefore the rates of vaccination and media awareness should be heightened in order to reduce the outbreak size and duration. Evidently, the effect of media awareness is higher in the control of cholera and hence,

it should be applied from the start of an outbreak in order to pare the transmission of cholera in any population.

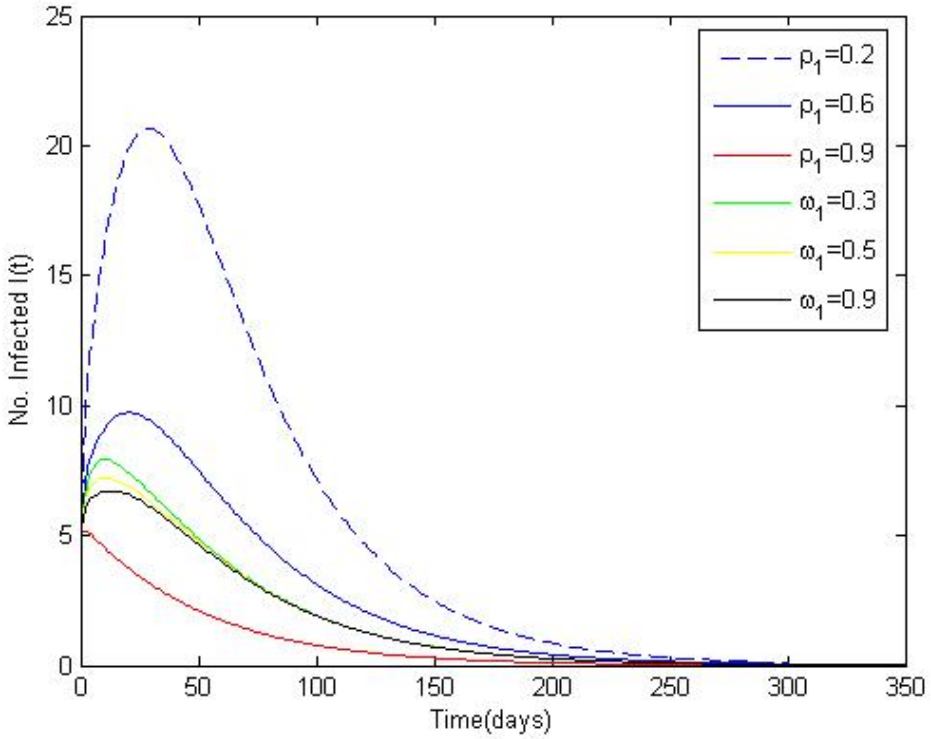

Figure 3.3: The Rate of Infection when Varying ρ and ω.

It is also evident from Figure 3.4 that vaccination and media awareness lower the disease spread with the first community experiencing earlier disease extinction. This clearly illustrates that the effects of the intervention strategies are unidentical in the two communities and that movement across the communities will lead to re-introduction of the disease in the community where it had been eradicated.

It is evident from Figures 3.5 and 3.6, that migration affects the rate of change of the infected population since, when the rate of movement into

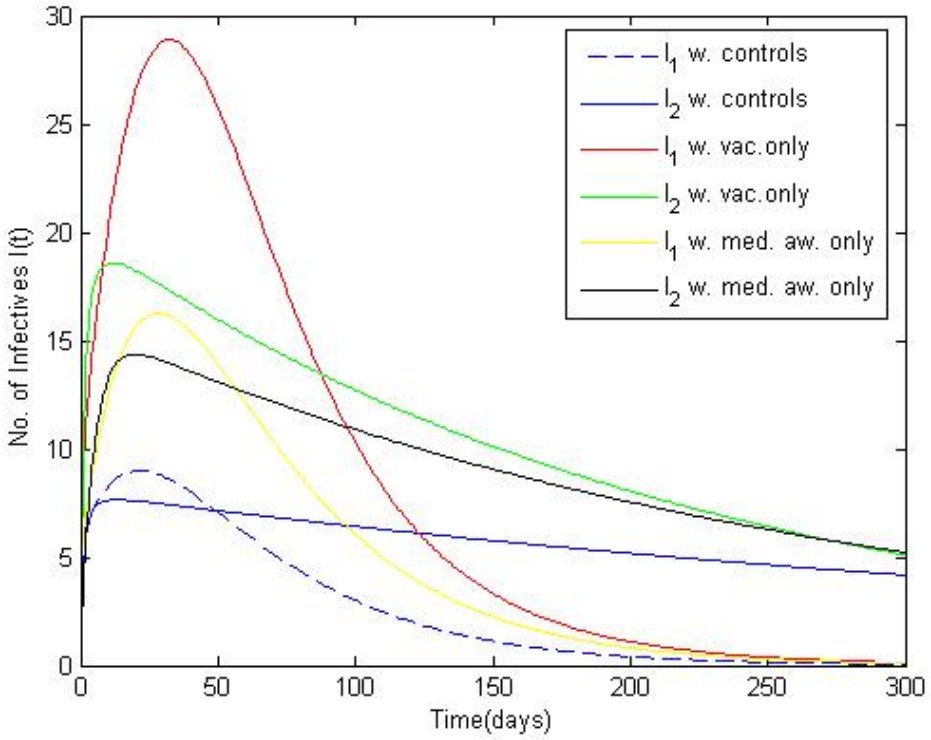

Figure 3.4: The Rate of Infection in the two Communities.

the first/second community is higher than the movement out, then the rate of change of the infected individuals increases and vice versa. This attests the fact that migration is a vital factor in the transmission of cholera and hence, movement across cholera hit communities should be circumvented.

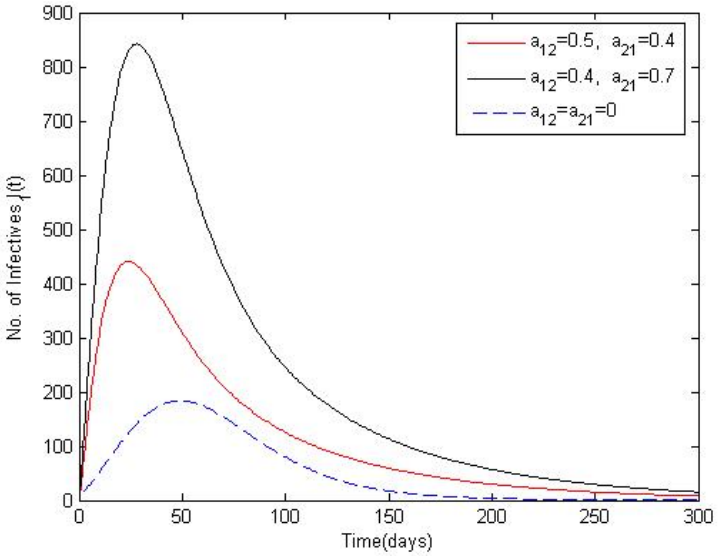

Figure 3.5: The Rate of Change of the Infectives (I_1) when Varying the Migration Parameters.

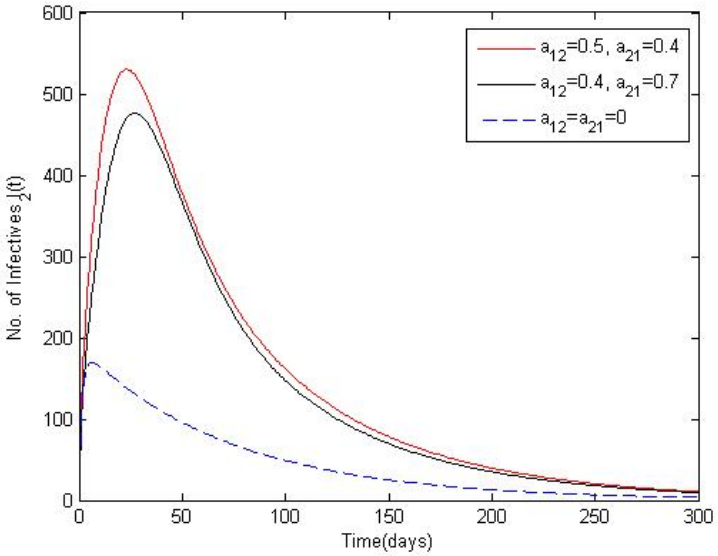

Figure 3.6: The Rate of Change of the Infectives (I_2) when Varying the Migration Parameters.

Chapter 4

Conclusion and Recommendation

4.1 Conclusion

In this study, a metapopulation model for cholera with imperfect vaccine and variable media awareness was developed and analysed. A mathematical model for Cholera transmission dynamics between two communities linked via migration was formulated. This was done to investigate the long term transmission dynamics of cholera, in the presence of these control strategies.

The analytical results of the model indicated that there is a region where the model is mathematically and epidemiologically well posed since its solutions were positive and bounded. The vaccine reproduction numbers for the two isolated communities were computed using the next generation matrix approach. It was also shown that there was no disease transmission when the reproduction numbers were below unity.

Stability analysis of the model exhibited that the disease free equilibrium

is both locally and globally asymptotically stable when $R_{Vi} < 1$. This implies that the spread of cholera reduces when R_{Vi} is below unity. The model was shown to have four endemic equilibria which were shown to be locally asymptotically stable when $R_{Vi} > 1$. Ideally, this means that the disease will persist in the community when R_{Vi} is greater than unity.

Sensitivity analysis of the model depicted that a reduction in the rate of ingestion of environmental *Vibrios*, the contact rate between the susceptibles and the infected, the shedding rate of *Vibrios* by the infected individuals, the multiplication rate of the pathogens and the recruitment of the susceptibles consequently results into a decrease of the reproduction number and the disease spread. Comparatively, an increase in the rate of vaccination, vaccine efficacy, media awareness efficacy, half saturation constant of the pathogen population enough to make an individual contract the infection, rate of recovery and decay rate of the *Vibrios*, similarly results in a decrease of the reproduction number and the disease spread. From the numerical simulations, it was evident that migration of the infected individuals across communities during epidemics, greatly increased the spread of cholera in the two communities. Evidently, effective media awareness and vaccination have also been shown to lower the disease spread resulting into a faster elimination of cholera in the two communities with the first community experiencing earlier disease extinction. This asserts that, the effects of these intervention strategies are unidentical in the two communities and that even with imperfect vaccine, the spread of cholera is greatly pared.

4.2 Recommendation

The findings of this study illustrates that cholera spreads faster when there is no or inefficient vaccination and media reporting about an outbreak and that the effects of the intervention strategies are unidentical in the two communities. Due to the endemicity of cholera in most African countries, we recommend that policy makers and health practitioners design and implement community specific intervention strategies with high efficacy levels.

As a future work, optimal control and cost effectiveness of vaccination and media awareness can be explored to determine the intervention strategy with the least cost and highest efficiency.

References

[1] Musundi B. O., Lawi G. O. and Nyamwala F. O. *Mathematical Analysis of a Cholera Transmission Model Incorporating Media Coverage.* International Journal of pure and Applied Mathematics. Vol. 111, No. 2, (2016), pp 219 − 231.

[2] Cholera: *Vibrio cholerae* infection in Africa. Available at www.cdc.gov

[3] Cholera's Seven Pandemics. Canadian Broadcasting cooperation December 2, 2008 Retrieved January 3, 2019

[4] Hays J. N. *Epidemics and pandemics; Their impacts on human history.* ABC-CLIO. ISBN 9781851096589

[5] Byrne and Joseph P. *Encyclopedia of Pestilence, Pandemics and Plagues: A-M* ABC-CLIO. 2008 p. 107 ISBN 978-0-313-34102-1

[6] Ministry of Health. *Multi-Sectoral Cholera Prevention and Control Plan* 2013-2018

[7] WHO. *Cholera Vaccines: WHO Position Paper - August 2017.* Weekly Epidemiological Record. 92(34): pp 477 − 500. 25_{th} August 2017.

[8] Cholera Vaccines: *WHO Position Paper.* Weekly epidemiological Rec. 2010 : 85(13) : 117

[9] Sur D. et al. *Efficacy and safety of a modified killed-whole-cell oral cholera vaccine in India: an interim analysis of a cluster-randomised,*

double-blind, placebo-controlled trial. Environmental Microbiology. Vol. 374(7902)(2009), pp 1694-1702.

[10] Marcelino E. S. et. al. *Effectiveness of mass cholera vaccination in Beira, Mozambique.* The New England Journal of Medicine. Vol. 352 *No.*8 (2005)

[11] Water.org *Kenya's Water and Sanitation Crisis* 2021 Water.org 501(c)(3) non-profit organization EIN: 58-2060131

[12] UN-Habitat *United Nations Human Settlements Programme (UN-Habitat). UN-Habitat Support to Sustainable Urban Development in Kenya: Addressing Urban Informality.* (2016). Available online: https://unhabitat.org/sites/ default/files/download-manager-files/UN-Habitat(accessed on 21 June 2020).

[13] Ana P. L., Cristiana J. S. and Delfim F. M. T. *A Cholera Mathematical Model with Vaccination and the Biggest Outbreak of World's History.* AIMS Mathematics. Vol. 3 No. 4. (2018) pp 448 − 463

[14] Harris J. B. *Cholera: Immunity and Prospects in Vaccine Development.* The Journal of Infectious Diseases, Vol. 218, (2018) pp 141-146.

[15] Nelson E., Harris J., Morris J., Calderwood S. and Camilli A., *Cholera Transmission: The Host, Pathogen and Bacteriophage Dynamics.* Nature Reviews. Microbiology.7(10), (2009) pp 693 − 702: doi:10.1038/nrmicro2204

[16] Codeco C. *Endemic and Epidemic Dynamics of cholera: The Role of the Aquatic Reservoir.* BMC Infectious diseases, Vol. 1, No. 1 (2001). DOI:10.1186/1471-2334-1-1.

[17] Sanches R. P., Ferreira C. P. and Kraenkel R. A. *The Role of Immunity and Seasonality in Cholera Epidemics,* Bulletin of Mathematical Biology, Vol. 73, No. 12, (2011) pp. 2916-2931.

[18] Jing'an C., Zhanmin W. and Xueyong Z. *Mathematical Analysis of a Cholera Model with Vaccination.* Journal of Applied Mathematics. Article ID 324767, (2014)

[19] Hellen N., Emmanuel O. and Livingstone L. *Modeling Optimal Control of Cholera Disease Under the Interventions of Vaccination, Treatment and Education Awareness.* Journal of Mathematics Research. Vol. 10 No. 5, (2018).

[20] Nneamaka J. E., Alain T. H. and Edwin M. *Modeling and Analysis of Cholera Dynamics with Vaccination.*" American Journal of Applied Mathematics and Statistics, Vol. 7, No. 1 (2019) pp 1 - 8. Doi: 10.12691/ajams-7-1-1.

[21] Huitao Z., Yiping L. and Yunxian D. *An SIRS Epidemic Model Incorporating Media Coverage with Time Delay:* Computational and Mathematical Methods in Medicine. Article ID 680743, (2014), 10 pages.

[22] Liao S. and Yang W. *Cholera Model Incorporating Media Coverage with Multiple Delays.* Mathematical Methods in the Applied Sciences. Vol. 42, (2019) pp 419 − 439.

[23] Fulford G. R., Roberts M. G. and Heasterback J. A. P. *The Metapopulation Dynamics of an infectious Disease: Tuberculosis in possums.* Theoritical Population Biology. Vol. 61, (2002), pp 15 − 29, *Doi* : 10.1006/*tpbi*.2001.1553,

[24] Njagarah J. B. H. and Nyabadza F., *A metapopulation model for cholera transmission dynamics between communities linked by migration.* Applied Mathematics and Computation. Vol. 241, (2014), pp $317 - 331$.

[25] The Telegraph News. *Migration behind introduction of cholera to Yemen, study finds.* 2nd January 2019.

[26] Leopard C. M., Damian K. and Emmanuel A. M. *Modeling and Stability Analysis for Measles Metapopulation Model with Vaccination.* Applied and Computational Mathematics. Vol. 4(6), (2015) pp $431 - 444$

[27] Njagarah J. B. H. and Nyabadza F. *Modelling Optimal Control of Cholera in Communities Linked by Migration:* Computational and Mathematical Methods in Medicine. Article ID 898264, (2015) 12 pages.

[28] P. van den Driessche and James W. *Reproduction numbers and subthreshold endemic equilibria for compartmental models of disease transmission.* Mathematical Biosciences. Vol. 180, No. $1 - 2$, (2002), pp $29 - 48$

[29] Castillo-Chavez C., Feng Z. and Huang W. *On the Computaion of R_0 and its Role on Global Stability.* Mathematical Approaches for Emerging and Reemerging Infectious Diseases. Vol. 125, (2002), pp $229 - 250$. Doi:10.1007/978-1-4757-3667-0-13.

[30] Wang J. and Charairat M. *Modeling Cholera Dynamics with Controls.* Canadian Applied Mathematics Quarterly. Vol. 19(3), (2011).

[31] Nyaberi H. O. and Malonza D. M. *Mathematical Model of Cholera Transmission with Education Campaign and Treatment Through Quar-*

antine. Journal of Advances in Mathematics and Computer Science. Vol. 32(3), No. 48942. (2019), pp 1-12.

[32] Yanli M., Jia-Bao L. and Haixia L. *Global Dynamics of an SIQR Model with Vaccination and Elimination Hybrid Strategies.* Mathematics Vol. 328 (6), (2018).

[33] Al-arydah M., Mwasa A., Tchuenche J. M., et al. *Modelling cholera disease with education and chlorination.* Journal of Biological System. Vol. 21(4), (2013), pp 1340007-20.

[34] Jennifer M. A., Farai N. and Josiah M. *Modelling cholera transmission dynamics in the presence of limited resources.* BMC Research Notes. Vol. 12 No. 475, (2019).

Appendix

MATLAB Codes used in the Simulation of the Metapopulation Cholera Model

clear

options=odeset('RelTol',1e-4,'AbsTol',[1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4]);

[T1,Y1]=ode45('nat1',[0:1:300],[10000,100,5,100,0,10000,100,5,100,0],options);
[T2,Y2]=ode45('nat2',[0:1:300],[10000,100,5,100,0,10000,100,5,100,0],options);
[T3,Y3]=ode45('nat3',[0:1:300],[10000,100,5,100,0,10000,100,5,100,0],options);
[T4,Y4]=ode45('nat4',[0:1:300],[10000,100,5,100,0,10000,100,5,100,0],options);

plot(T1,Y1(:,3),'–',T2,Y2(:,3),'-b',T3,Y3(:,3),'-r',T4,Y4(:,3),'-g');

xlabel 'Time(days)'; ylabel 'No. Infected I(t)';

clear

options=odeset('RelTol',1e-4,'AbsTol',[1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4]);

[T1,Y1]=ode45('nat1',[0:1:200],[10000,100,5,100,0,10000,100,5,100,0],options);
[T2,Y2]=ode45('nat2',[0:1:200],[10000,100,5,100,0,10000,100,5,100,0],options);
[T3,Y3]=ode45('nat3',[0:1:200],[10000,100,5,100,0,10000,100,5,100,0],options);
[T4,Y4]=ode45('nat4',[0:1:200],[10000,100,5,100,0,10000,100,5,100,0],options);

plot(T1,Y1(:,4),'–',T2,Y2(:,4),'-b',T3,Y3(:,4),'-r',T4,Y4(:,4),'-g');

xlabel 'Time(days)'; ylabel 'Concentration of *Vibrios* B(t)';

clear

options=odeset('RelTol',1e-4,'AbsTol',[1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4]);

[T5,Y5]=ode45('nat7',[0:1:300],[10000,100,5,100,0,10000,100,5,100,0],options);
[T6,Y6]=ode45('nat8',[0:1:300],[10000,100,5,100,0,10000,100,5,100,0],options);
[T7,Y7]=ode45('nat9',[0:1:300],[10000,100,5,100,0,10000,100,5,100,0],options);
[T8,Y8]=ode45('nat10',[0:1:350],[10000,100,5,100,0,10000,100,5,100,0],options);
[T9,Y9]=ode45('nat11',[0:1:350],[10000,100,5,100,0,10000,100,5,100,0],options);
[T10,Y10]=ode45('nat12',[0:1:350],[10000,100,5,100,0,10000,100,5,100,0],options);

plot(T5,Y5(:,3),'–',T6,Y6(:,3),'-b',T7,Y7(:,3),'-r',T8,Y8(:,3),'-g',T9,Y9(:,3),'-y',T10,Y10(:,3),'-k');

xlabel 'Time(days)'; ylabel 'No. Infected I(t)';

clear

options=odeset('RelTol',1e-4,'AbsTol',[1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4]);

[T4,Y4]=ode45('nat22',[0:1:300],[10000,100,5,100,0,1000,10,1,50,0],options);
[T5,Y5]=ode45('nat24',[0:1:300],[10000,100,5,100,0,1000,10,1,50,0],options);
[T6,Y6]=ode45('nat25',[0:1:300],[10000,100,5,100,0,1000,10,1,50,0],options);

plot(T4,Y4(:,3),'–',T4,Y4(:,8),'-b',T5,Y5(:,3),'-r',T5,Y5(:,8),'-g',T6,Y6(:,3),'-y',T6,Y6(:,8),'-k');

xlabel 'Time(days)'; ylabel 'No. of Infectives I(t)';

clear

options=odeset('RelTol',1e-4,'AbsTol',[1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4]);

[T3,Y3]=ode45('nat26',[0:1:300],[10000,100,5,100,0,10000,100,5,100,0],options);
[T4,Y4]=ode45('nat27',[0:1:300],[10000,100,5,100,0,10000,100,5,100,0],options);

plot(T3,Y3(:,3),'-r',T4,Y4(:,3),'-k',T1,Y1(:,3),'–');

xlabel 'Time(days)'; ylabel 'No. of Infectives $I_1(t)$'; 2‘1 qS=] 784 05 **clear**

options=odeset('RelTol',1e-4,'AbsTol',[1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4]);

[T1,Y1]=ode45('nat28',[0:1:300],[10000,100,5,100,0,10000,100,5,100,0],options);
[T3,Y3]=ode45('nat26',[0:1:300],[10000,100,5,100,0,10000,100,5,100,0],options);
[T4,Y4]=ode45('nat27',[0:1:300],[10000,100,5,100,0,10000,100,5,100,0],options);

plot(T3,Y3(:,8),'-r',T4,Y4(:,8),'-k',T1,Y1(:,8),'–');

xlabel 'Time(days)'; ylabel 'No. of Infectives $I_2(t)$';

clear

options=odeset('RelTol',1e-4,'AbsTol',[1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4 1e-4]);

[T1,Y1]=ode45('nat28',[0:1:300],[10000,100,5,100,0,10000,100,5,100,0],options);
[T3,Y3]=ode45('nat26',[0:1:300],[10000,100,5,100,0,10000,100,5,100,0],options);
[T4,Y4]=ode45('nat27',[0:1:300],[10000,100,5,100,0,10000,100,5,100,0],options);

subplot(2,2,1) plot(T3,Y3(:,3),'-r',T4,Y4(:,3),'-k',T1,Y1(:,3),'–'); title('a');
xlabel 'Time(days)'; ylabel 'No. of Infectives $I_1(t)$'; hold on

subplot(2,2,2) plot(T3,Y3(:,8),'-r',T4,Y4(:,8),'-k',T1,Y1(:,8),'–'); title('b');
xlabel 'Time(days)'; ylabel 'No. of Infectives $I_2(t)$'; hold off

function dy=nat1(t,y)

Lambda1=9.6274*10e-5; omega1=0.78; rho1=0.75; betae1=0.075; betah1=0.0005; kappa=1000000; m=0.00001; sigma1=0.68; mu1=0.02; gamma1=0.015; delta1=0.013; xi1=50; mu1p=1.06 g1=0.73 Lambda2=9.6274*10e-5; omega2=0.7; rho2=0.8; betae2=0.01694; betah2=0.0125; sigma2=0.5; mu2=5.48*10e-5; gamma2=0.2; delta2=4.0*10e-4; xi2=50; mu2p=1.06; g2=0.73;

dy=[0 0 0 0 0 0 0 0 0 0]';

dy(1)=Lambda1-omega1*y(1)-((1-rho1)*betae1*y(4)*y(1))/(kappa+y(4))-((1-rho1)*betah1*y(3)*y(1)/(m+y(3)))-mu1*y(1);

dy(2)=omega1*y(1)-((1-sigma1)*(1-rho1)*betae1*y(4)*y(2))/(kappa+y(4))-((1-sigma1)*(1-rho1)*betah1*y(3)*y(2))/(m+y(3))-mu1*y(2);

dy(3)=((1-rho1)*betae1*y(4)*y(1))/(kappa+y(4))+((1-rho1)*betah1*y(3)*y(1))/(m+y(3))+((1-sigma1)*(1-rho1)*betae1*y(4)*y(2))/(kappa+y(4))+((1-sigma1)*(1-rho1)*betah1*y(3)*y(2))/(m+y(3))-(mu1+delta1+gamma1)*y(3);

dy(4)=(1-rho1)*xi1*y(3)-(mu1p-g1)*y(4);

dy(5)=gamma1*y(3)-mu1*y(5);

dy(6)=Lambda2-omega2*y(6)-((1-rho2)*betae2*y(9)*y(6))/(kappa+y(9))-((1-rho2)*betah2*y(8)*y(6)/(m+y(8)))-mu2*y(6);

dy(7)=omega2*y(6)-((1-sigma2)*(1-rho2)*betae2*y(9)*y(7))/(kappa+y(9))-((1-sigma2)*(1-rho2)*betah2*y(8)*y(7))/(m+y(8))-mu2*y(7);

dy(8)=((1-rho2)*betae2*y(9)*y(6))/(kappa+y(9))+((1-rho2)*betah2*y(8)*y(6))/(m+y(8))+((1-sigma2)*(1-rho2)*betae2*y(9)*y(7))/(kappa+y(9))+ ((1-sigma2)*(1-rho2)*betah2*y(8)*y(7))/(m+y(8))-(mu2+delta2+gamma2)*y(8);

dy(9)=(1-rho2)*xi2*y(8)-(mu2p-g2)*y(9);

dy(10)=gamma2*y(8)-mu2*y(10);

function dy=nat2(t,y)

Lambda1=9.6274*10e-5; omega1=0; rho1=0; betae1=0.075; betah1=0.0005; kappa=1000000; m=0.00001; sigma1=0; mu1=0.02; gamma1=0.015; delta1=0.013; xi1=50; mu1p=1.06 g1=0.73 Lambda2=9.6274*10e-5; omega2=0.7; rho2=0.8; betae2=0.01694; betah2=0.0125; sigma2=0.5; mu2=5.48*10e-5; gamma2=0.2; delta2=4.0*10e-4; xi2=50; mu2p=1.06; g2=0.73;

dy, dy(1), dy(2), dy(3), dy(4), dy(5), dy(6), dy(7), dy(8), dy(9), and dy(10) are the same as in **function dy=nat1(t,y)**

function dy=nat3(t,y)

Lambda1=9.6274*10e-5; omega1=0.78; rho1=0; betae1=0.075; betah1=0.0005; kappa=1000000; m=0.00001; sigma1=0.68; mu1=0.02; gamma1=0.015; delta1=0.013; xi1=50; mu1p=1.06 g1=0.73 Lambda2=9.6274*10e-5; omega2=0.7; rho2=0.8; betae2=0.01694; betah2=0.0125; sigma2=0.5; mu2=5.48*10e-5; gamma2=0.2; delta2=4.0*10e-4; xi2=50; mu2p=1.06; g2=0.73;

dy, dy(1), dy(2), dy(3), dy(4), dy(5), dy(6), dy(7), dy(8), dy(9), and dy(10) are the same as in **function dy=nat1(t,y)**

function dy=nat4(t,y)

Lambda1=9.6274*10e-5; omega1=0; rho1=0.75; betae1=0.075; betah1=0.0005; kappa=1000000; m=0.00001; sigma1=0; mu1=0.02; gamma1=0.015; delta1=0.013; xi1=50; mu1p=1.06 g1=0.73 Lambda2=9.6274*10e-5; omega2=0.7; rho2=0.8; betae2=0.01694; betah2=0.0125; sigma2=0.5; mu2=5.48*10e-5; gamma2=0.2; delta2=4.0*10e-4; xi2=50; mu2p=1.06; g2=0.73;

dy, dy(1), dy(2), dy(3), dy(4), dy(5), dy(6), dy(7), dy(8), dy(9), and dy(10) are the same as in **function dy=nat1(t,y)**

function dy=nat7(t,y)

Lambda1=9.6274*10e-5; omega1=0.78; rho1=0.2; betae1=0.075; betah1=0.0005; kappa=1000000; m=0.00001; sigma1=0.68; mu1=0.02; gamma1=0.015; delta1=0.013; xi1=50; mu1p=1.06 g1=0.73 Lambda2=9.6274*10e-5; omega2=0.7; rho2=0.8; betae2=0.01694; betah2=0.0125; sigma2=0.5; mu2=5.48*10e-5; gamma2=0.2; delta2=4.0*10e-4; xi2=50; mu2p=1.06; g2=0.73;

dy, dy(1), dy(2), dy(3), dy(4), dy(5), dy(6), dy(7), dy(8), dy(9), and dy(10) are the same as in **function dy=nat1(t,y)**

function dy=nat8(t,y)

Lambda1=9.6274*10e-5; omega1=0.78; rho1=0.6; betae1=0.075; betah1=0.0005; kappa=1000000; m=0.00001; sigma1=0.68; mu1=0.02; gamma1=0.015; delta1=0.013; xi1=50; mu1p=1.06 g1=0.73 Lambda2=9.6274*10e-5; omega2=0.7; rho2=0.8; betae2=0.01694; betah2=0.0125; sigma2=0.5; mu2=5.48*10e-5; gamma2=0.2; delta2=4.0*10e-4; xi2=50; mu2p=1.06; g2=0.73;

dy, dy(1), dy(2), dy(3), dy(4), dy(5), dy(6), dy(7), dy(8), dy(9), and dy(10) are the same as in **function dy=nat1(t,y)**

function dy=nat9(t,y)

Lambda1=9.6274*10e-5; omega1=0.78; rho1=0.9; betae1=0.075; betah1=0.0005; kappa=1000000; m=0.00001; sigma1=0.68; mu1=0.02; gamma1=0.015; delta1=0.013; xi1=50; mu1p=1.06 g1=0.73 Lambda2=9.6274*10e-5; omega2=0.7; rho2=0.8; betae2=0.01694; betah2=0.0125; sigma2=0.5; mu2=5.48*10e-5; gamma2=0.2; delta2=4.0*10e-4; xi2=50; mu2p=1.06; g2=0.73;

dy, dy(1), dy(2), dy(3), dy(4), dy(5), dy(6), dy(7), dy(8), dy(9), and dy(10) are the same as in **function dy=nat1(t,y)**

function dy=nat10(t,y)

Lambda1=9.6274*10e-5; omega1=0.3; rho1=0.75; betae1=0.075; betah1=0.0005; kappa=1000000; m=0.00001; sigma1=0.68; mu1=0.02; gamma1=0.015; delta1=0.013; xi1=50; mu1p=1.06 g1=0.73 Lambda2=9.6274*10e-5; omega2=0.7; rho2=0.8; betae2=0.01694; betah2=0.0125; sigma2=0.5; mu2=5.48*10e-5; gamma2=0.2; delta2=4.0*10e-4; xi2=50; mu2p=1.06; g2=0.73;

dy, dy(1), dy(2), dy(3), dy(4), dy(5), dy(6), dy(7), dy(8), dy(9), and dy(10) are the same as in **function dy=nat1(t,y)**

function dy=nat11(t,y)

Lambda1=9.6274*10e-5; omega1=0.5; rho1=0.75; betae1=0.075; betah1=0.0005; kappa=1000000; m=0.00001; sigma1=0.68; mu1=0.02; gamma1=0.015; delta1=0.013; xi1=50; mu1p=1.06 g1=0.73 Lambda2=9.6274*10e-5; omega2=0.7; rho2=0.8; betae2=0.01694; betah2=0.0125; sigma2=0.5; mu2=5.48*10e-5; gamma2=0.2; delta2=4.0*10e-4; xi2=50; mu2p=1.06; g2=0.73;

dy, dy(1), dy(2), dy(3), dy(4), dy(5), dy(6), dy(7), dy(8), dy(9), and dy(10) are the same as in **function dy=nat1(t,y)**

function dy=nat12(t,y)

Lambda1=9.6274*10e-5; omega1=0.9; rho1=0.75; betae1=0.075; betah1=0.0005; kappa=1000000; m=0.00001; sigma1=0.68; mu1=0.02; gamma1=0.015; delta1=0.013; xi1=50; mu1p=1.06 g1=0.73 Lambda2=9.6274*10e-5; omega2=0.7; rho2=0.8; betae2=0.01694; betah2=0.0125; sigma2=0.5; mu2=5.48*10e-5; gamma2=0.2; delta2=4.0*10e-4; xi2=50; mu2p=1.06; g2=0.73;

dy, dy(1), dy(2), dy(3), dy(4), dy(5), dy(6), dy(7), dy(8), dy(9), and dy(10) are the same as in **function dy=nat1(t,y)**

function dy=nat22(t,y)

Lambda1=9.6274*10e-5; omega1=0.78; rho1=0.75; betae1=0.075; betah1=0.0005; kappa=1000000; m=0.00001; sigma1=0.5; mu1=0.02; gamma1=0.015; delta1=0.013; xi1=50; mu1p=1.06 g1=0.73 Lambda2=9.6274*10e-5; omega2=0.8; rho2=0.6; betae2=0.01694; betah2=0.0125; sigma2=0.68; mu2=5.48*10e-5; gamma2=0.2; delta2=4.0*10e-4; xi2=50; mu2p=1.06; g2=0.73;

dy, dy(1), dy(2), dy(3), dy(4), dy(5), dy(6), dy(7), dy(8), dy(9), and dy(10) are the same as in **function dy=nat1(t,y)**

function dy=nat24(t,y)

Lambda1=9.6274*10e-5; omega1=0.78; rho1=0; betae1=0.075; betah1=0.0005; kappa=1000000; m=0.00001; sigma1=0.68; mu1=0.02; gamma1=0.015; delta1=0.013; xi1=50; mu1p=1.06 g1=0.73 Lambda2=9.6274*10e-5; omega2=0.78; rho2=0; betae2=0.01694; betah2=0.0125; sigma2=0.68; mu2=5.48*10e-5; gamma2=0.2; delta2=4.0*10e-4; xi2=50; mu2p=1.06; g2=0.73;

dy, dy(1), dy(2), dy(3), dy(4), dy(5), dy(6), dy(7), dy(8), dy(9), and dy(10) are the same as in **function dy=nat1(t,y)**

function dy=nat25(t,y)

Lambda1=9.6274*10e-5; omega1=0; rho1=0.75; betae1=0.075; betah1=0.0005; kappa=1000000; m=0.00001; sigma1=0; mu1=0.02; gamma1=0.015; delta1=0.013; xi1=50; mu1p=1.06 g1=0.73 Lambda2=9.6274*10e-5; omega2=0; rho2=0.75; betae2=0.01694; betah2=0.0125; sigma2=0; mu2=5.48*10e-5; gamma2=0.2; delta2=4.0*10e-4; xi2=50; mu2p=1.06; g2=0.73;

dy, dy(1), dy(2), dy(3), dy(4), dy(5), dy(6), dy(7), dy(8), dy(9), and dy(10) are the same as in **function dy=nat1(t,y)**

function dy=nat26(t,y)

Lambda1=9.6274*10e-5; omega1=0.8; rho1=0; betae1=0.075; betah1=0.0005; kappa=1000000; m=0.00001; sigma1=0; mu1=0.02; gamma1=0.015; delta1=0.013; xi1=50; mu1p=1.06 g1=0.73 Lambda2=9.6274*10e-5; omega2=0; rho2=0; betae2=0.01694; betah2=0.0125; sigma2=0.5; mu2=5.48*10e-5; gamma2=0.2; delta2=4.0*10e-4; xi2=50; mu2p=1.06; g2=0.73; a12=0.5; a21=0.4;

dy=[0 0 0 0 0 0 0 0 0 0]';

dy(1)=Lambda1-omega1*y(1)-((1-rho1)*betae1*y(4)*y(1))/(kappa+y(4))-((1-rho1)*betah1*y(3)*y(1)/(m+y(3)))-mu1*y(1);

dy(2)=omega1*y(1)-((1-sigma1)*(1-rho1)*betae1*y(4)*y(2))/(kappa+y(4))-((1-sigma1)*(1-rho1)*betah1*y(3)*y(2))/(m+y(3))-mu1*y(2);

dy(3)=((1-rho1)*betae1*y(4)*y(1))/(kappa+y(4))+((1-rho1)*betah1*y(3)*y(1))/(m+y(3))+((1-sigma1)*(1-rho1)*betae1*y(4)*y(2))/(kappa+y(4))+ ((1-sigma1)*(1-rho1)*betah1*y(3)*y(2))/(m+y(3))+a21*y(8)-(mu1+delta1+gamma1+a12)*y(3);

dy(4)=(1-rho1)*xi1*y(3)-(mu1p-g1)*y(4);

dy(5)=gamma1*y(3)-mu1*y(5);

dy(6)=Lambda2-omega2*y(6)-((1-rho2)*betae2*y(9)*y(6))/(kappa+y(9))-((1-rho2)*betah2*y(8)*y(6)/(m+y(8)))-mu2*y(6);

dy(7)=omega2*y(6)-((1-sigma2)*(1-rho2)*betae2*y(9)*y(7))/(kappa+y(9))-((1-sigma2)*(1-rho2)*betah2*y(8)*y(7))/(m+y(8))-mu2*y(7);

dy(8)=((1-rho2)*betae2*y(9)*y(6))/(kappa+y(9))+((1-rho2)*betah2*y(8)*y(6))/(m+y(8))+((1-sigma2)*(1-rho2)*betae2*y(9)*y(7))/(kappa+y(9))+ ((1-sigma2)*(1-rho2)*betah2*y(8)*y(7))/(m+y(8))+a12*y(3)-(mu2+delta2+gamma2+a21)*y(8);

dy(9)=(1-rho2)*xi2*y(8)-(mu2p-g2)*y(9);

dy(10)=gamma2*y(8)-mu2*y(10);

function dy=nat27(t,y)

Lambda1=9.6274*10e-5; omega1=0.8; rho1=0; betae1=0.075; betah1=0.0005; kappa=1000000; m=0.00001; sigma1=0; mu1=0.02; gamma1=0.015; delta1=0.013; xi1=50; mu1p=1.06 g1=0.73 Lambda2=9.6274*10e-5; omega2=0; rho2=0; betae2=0.01694; betah2=0.0125; sigma2=0.5; mu2=5.48*10e-5; gamma2=0.2; delta2=4.0*10e-4; xi2=50; mu2p=1.06; g2=0.73; a12=0.4; a21=0.7;

dy, dy(1), dy(2), dy(3), dy(4), dy(5), dy(6), dy(7), dy(8), dy(9), and dy(10) are the same as in **function dy=nat26(t,y)**

function dy=nat28(t,y)

Lambda1=9.6274*10e-5; omega1=0.8; rho1=0; betae1=0.075; betah1=0.0005; kappa=1000000; m=0.00001; sigma1=0; mu1=0.02; gamma1=0.015; delta1=0.013; xi1=50; mu1p=1.06 g1=0.73 Lambda2=9.6274*10e-5; omega2=0; rho2=0;

betae2=0.01694; betah2=0.0125; sigma2=0.5; mu2=5.48*10e-5; gamma2=0.2; delta2=4.0*10e-4; xi2=50; mu2p=1.06; g2=0.73; a12=0; a21=0;

dy, dy(1), dy(2), dy(3), dy(4), dy(5), dy(6), dy(7), dy(8), dy(9), and dy(10) are the same as in **function dy=nat26(t,y)**